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The Journal of Pediatric Research

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Prof. Dr. Yavuz Anacak

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Özgür Çoğulu

Ege University, Faculty of Medicine, Department of Pediatrics, İzmir, Turkey
E-posta: ozgur.cogulu@ege.edu.tr
ORCID ID: orcid.org/0000-0002-9037-5599

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Özgür Çoğulu

Ege University Faculty of Medicine, Department of Pediatrics, İzmir, Turkey
ozgur.cogulu@ege.edu.tr
orcid.org/0000-0002-9037-5599

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34093 İstanbul, Türkiye
Phone: +90 (212) 621 99 25 **Fax:** +90 (212) 621 99 27
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Address for Correspondence

Özgür Çoğulu
Ege University Faculty of Medicine, Department of Pediatrics, Bornova, 35100 İzmir, Turkey
Phone: +90 232 390 10 05 - 390 10 31
Fax: +90 232 390 13 57
E-mail: ozgur.cogulu@ege.edu.tr

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Editor: Özgür Çoğulu
Ege University Faculty of Medicine, Department of Pediatrics, Bornova, 35100 İzmir, Turkey
Phone: +90 232 390 10 05 - 390 10 31
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Galenos Yayınevi Tic. Ltd. Şti.
Molla Gürani Mah. Kaçamak Sok. No: 21/1
34093, İstanbul, Turkey
Phone: +90 212 621 99 25
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PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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All results of data and analysis should be presented in the Results section as tables, figures and graphics; biostatistical methods used and application details should be presented in the Materials and Methods section or under a separate title.

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Conclusion: Should summarize the results of the study, the clinical applicability of the results should be defined, and the favorable and unfavorable aspects should be declared.

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Study Limitations: Limitations of the study should be discussed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

Conclusion: The conclusion of the study should be highlighted.

Acknowledgements: Any technical or financial support or editorial contributions (statistical analysis, English evaluation) towards the study should appear at the end of the article.

References: Authors are responsible for the accuracy of the references. See General Guidelines for details about the usage and formatting required.

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Case reports should present cases which are rarely seen, feature novelty in diagnosis and treatment, and contribute to our current knowledge. The first page should include the title in English, an unstructured summary not exceeding 50 words, and key words. The main text should consist of introduction, case report, discussion and references. The entire text should not exceed 1500 words (A4, formatted as specified above). A maximum of 10 references shall be used in case reports.

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Review articles can address any aspect of clinical or laboratory pediatry. Review articles must provide critical analyses of contemporary evidence and provide directions for future research. **The journal only accepts and publishes invited reviews.** Before sending a review, discussion with the editor is recommended.

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CORRESPONDENCE

Prof. Dr. Özgür Çoğulu

The Journal of Pediatric Research

Ege University Faculty of Medicine, Department of Pediatrics, Bornova, 35100 İzmir, Turkey

Phone: +90 232 390 10 05 - 390 10 31

Fax: +90 232 390 13 57

E-mail: ozgur.cogulu@ege.edu.tr

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Editorial

Dear Readers,

We are very happy to welcome you to the first issue of "*The Journal of Pediatric Research*" in 2018. May this new year bring peace, justice and happiness to the world.

"*The Journal of Pediatric Research*" makes a vibrant start to the year 2018. With the new format of our journal and the continuous support of all our readers, authors, and reviewers, we have come to a point where our journal will only be published in English from now on. We hope to reach a larger audience of readers and eventually to be listed in new indexes in addition to Web of Science-Emerging Sources Citation Index (ESCI), Directory of Open Access Journals (DOAJ), EBSCO, CINAHL Complete Database, ProQuest, Copernicus, Tübitak/Ulakbim TR Index, TurkMedline and Turkiye Citation Index.

In the first issue of 2018, we are delighted to present you with several remarkable works from different disciplines and countries from all over the world. Pain management strategies for venipuncture, experiences about hospitalized high risk children for varicella and lower respiratory tract infections and surgical management of congenital pulmonary airway malformations are among the original research articles in this issue that will provide unique clinical perspectives for our readers. In addition, we think original research articles on risk management in the pediatric emergency department, and the effects of Vitamin D on neonatal prognosis will get the attention of our readers in these scientifically hot topics.

I would like to acknowledge the members of our editorial board, reviewers, authors, and Galenos Publishing House for their magnificent support in preparing the first issue of 2018. It is a privilege to be a member of this great team and the editor of this issue as we are beginning a new era for our journal. We look forward to your scientific contributions in 2018 and hope you enjoy reading *The Journal of Pediatric Research*.

Cordially,

Özge Altun Köroğlu MD.,
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Original Article

Music Listening Intervention vs Local Anaesthetic Cream for Pain Management in Infants Undergoing Venepuncture: A Collaborative Trans-Disciplinary Research

Wen Fen Beh[1], Mohd Nasir Hashim[1], Wan Ju Tan[2], Zarina Abdul Latiff[3]

[1]*University of Malaya Cultural Centre, Department of Music, Kuala Lumpur, Malaysia*
[2]*Ministry of Health, Department of Pediatrics, Kuala Lumpur, Malaysia*
[3]*University Kebangsaan Malaysia Medical Centre, Department of Pediatrics, Kuala Lumpur, Malaysia*

ABSTRACT

Aim: Local anaesthetic cream (EMLA) is often used for paediatric procedural pain management. However, there are concerns about dependency on pain medication. A healthier alternative would be to use music listening intervention instead. This study aimed to test the effectiveness of music listening intervention in managing pain for infants undergoing venepuncture procedures in comparison to using EMLA.

Materials and Methods: The research was conducted in two phases-in the first phase, surveys were conducted to determine the spectrum of popular Malaysian folk songs for children in nursery schools, and the selection of songs was then rearranged in an instrumental form to be played in the experimental phase. The experimental phase is the second part which involved the focus and control groups of infants that required venepuncture procedures. The focus group was given music listening intervention during the procedure while the control group was given EMLA.

Results: The results revealed that there was no statistical difference between the two groups in pain management.

Conclusion: This study shows that music listening intervention is comparable to EMLA cream in the management of venepuncture pain based on physiological response and pain behavioural score.

Keywords: Music listening intervention, local anaesthetic cream, venepuncture, pain management, infants

Introduction

Human beings are surrounded and nourished by music from the moment of conception particularly through the strong rhythmic beat of the maternal heartbeat (1). Nature has also given mankind music through the sounds of rain and wind, running waters and rustling leaves, thus music and rhythm are inherent in our very being (2). Hence, our lives are invariably connected to some form of music (3). This very fact explains why music can be used as a form of therapy to soothe and calm the human momentum in experiencing stress or pain (4). Children are a vulnerable group (5). They are easily affected by their environment in many ways (6). Pain is an aspect where children tend to suffer because of their lower tolerance level (7). Thus, parents, medical doctors and caregivers should adopt child-friendly approaches which can help to lower the impact of pain on children whenever possible, especially during medical procedures (8). Some side effects of pain are acute while others are subliminal or even chronic (9). Side effects of pain can take a toll on parents especially when their young children become stressful and restless (10). Based on the observations of previous medical experiences, it is noted that every child carries his/her own complex recollection of pain, imagination, worries, and misinterpretation (11). As a result, the child's behaviour can cause family members a lot of anxiety (12). To

Address for Correspondence
Wen Fen Beh PhD, University of Malaya Cultural Centre, Department of Music, Kuala Lumpur, Malaysia
Phone: +601 653 009 55 E-mail: behwenfen@hotmail.com ORCID ID: orcid.org/0000-0002-2974-1000
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alleviate this momentum, medical practitioners may apply a local anaesthetic cream (EMLA) known as EMLA cream on paediatric patients in order to reduce their pain during medical procedures (13). According to the Gate Control Theory of Pain (14), physical pain often occurs in nerve endings throughout the entire body. However, the interpretation and awareness of the stimulation takes place in the central nervous system (CNS). Whilst this is happening, the CNS also takes in other stimuli which include auditory and visual stimuli. The CNS can only process a limited amount of information at any one time, and all these sensations are simultaneously competing with the pain stimulus for attention (15). As a result of this competition, the human perception of pain can be reduced due to the limited capacity of the conscious awareness. If the positive conscious awareness can be enhanced, the perception of pain can be weakened (16). In music listening intervention, the CNS can be positively enhanced by the music, thereby leading to a weakened perception of pain (17). According to Davis et al. (18), music can be used as a cognitive pain control strategy in the following ways: as a stimulus for active focus or distraction, as a cue for relaxation response, as a masking agent, and as a positive environment stimulus.

Music in the medical field has always existed in many forms in different cultures for centuries. It was around the mid-20th century that dependence on music as an alternative therapeutic intervention increased. Growing interests in music as an alternative for medical therapy has progressed through recent years (19-22). Music is often considered as a complementary therapy (23). Studies (20,21,24) have shown successful results of music intervention in a wide variety of clinical settings such as pain therapy, surgery and anaesthesia (25). The reason for music being used as an alternative intervention for pain therapy is that there are connections between music and the pain experienced by humans. Eagle and Harish (15) explained that both music and pain are alike in terms of frequency/pitch, intensity/loudness, wave form/timber, duration/time, and location/localization. By manipulating music in accordance with the connections, the body can be tricked to suppress pain and assist in pain therapy. This research aimed to investigate the effectiveness of music listening intervention for alleviating pain among children in comparison to the use of the EMLA cream, a eutectic mixture of lidocaine and prilocaine (26). One of its main characteristics is that it has good skin absorption making it a popular topical analgesic (27). Since the 1980's, EMLA has been a focus for medical and nursing research because of the concerns regarding paediatric procedural pain (28). Several studies have shown EMLA to be an effective local anaesthetic for paediatric venepuncture pain and for intramuscular injections (29). In a study conducted by Rogers and Ostrow (30), EMLA cream was compared with a placebo (31), iontophoresis, and amethocaine cream in decreasing venepuncture pain in children. The study showed that EMLA cream was an effective local anaesthetic for paediatric venepuncture pain during both intravenous cannulation and phlebotomy. It is safe and has relatively few side effects. Manufacturers recommend an application time of 60 minutes (13), applied in a mound over the venepuncture site, covered with a semi-permeable dressing. This process facilitates skin absorption which allows the anaesthetic agent to hinder initiation and conduction of nerve impulses that cause pain (32). Although EMLA cream is effective in reducing venepuncture pain in infants, its side effects include transient local blanching followed by erythema at the injection site (33). It is also time, energy and money-consuming (34). Unlike EMLA, music is a form of melody that surrounds the human activity and it is easily accessible through various forms of the media. If used as a substitute to alleviate pain, music, in comparison to EMLA, is low in cost, readily available and has no adverse effects (35,36). In the context of this study, pain experienced by the infant is medically treated with a topical cream, the EMLA cream. This cream is placed on the spot where the infant is deemed to be experiencing the pain. If music therapy is considered, then music will be played to the infants undergoing venepuncture procedure and as the rhythm plays, it will automatically replace the rhythm of the pain experienced by the infant.

Materials and Methods

Subjects

All the subjects involved in this study (n=30) were paediatric patients aged between 2 to 24 months. They were admitted to the general paediatric ward or day-care of a tertiary medical centre requiring venepuncture. Since the memory of children at that age is still at a developing phase, it is possible that they may be naive towards the procedures. It is because of this, Oehler (as cited in 37) suggests that music listening intervention may be able to calm them down more easily. Nonetheless, once they reach beyond 2 years of age, these children may become more aware of their surroundings, thus increasing their consciousness of the inadvertent pain during venepuncture (37). For this reason, only paediatric patients aged 2 to 24 months were selected for this research.

This study was approved by the Research Ethics Committee (REC) of University Kebangsaan Malaysia (UKM) (approval number: FF-264-2011). Consent was filled out and given by the parents and guardians of the participants.

Measure Instrument

Faces Pain Scale

According to Wong and Baker (38), the Faces Pain scale (FPS) is the most widely-used pain score for the assessment of pain via self-report. It comprises a single straight 100 mm line, and the extremes of the line denote the level of pain experienced with indications of "no pain" to "worst possible pain". Observer ratings of pain using the FPS showed good intra and inter-rater reliability, from 0.69-0.91 and 0.55-0.97 respectively. In the case of young children, the FPS was

developed in order to make it possible to score on the widely accepted 0 to 10 metric scale. There is a high correlation between FPS and the many different versions of the Faces scale; the Wong-Baker Pain scale is the most popular among both children and parents (39). The FPS has in fact been used in infants from 2 months up to 4 years old, and has been validated against the Modified Behavioural Pain Scale (MBPS) (40). Pain scoring for this study was done by using the Wong-Baker FPS, a scale consisting of 6 faces equivalent to a visual analogue score on a 10 cm numeric pain intensity scale. This instrument has been validated and is widely-used as a pain assessment scale (41). Figure 1 shows the standard measure for the FPS.

Modified Behavioural Pain Scale

According to Taddio et al. (40), the MBPS is a behavioural pain measure that examines responses from 3 domains: facial expression, crying, and body movements. The overall score (range, 0-10) comprises the sum of individual scores obtained from each domain. The reliability and validity of the MBPS for measuring acute pain in infants have been well demonstrated (42). Figure 2 shows the standard measurements for the MBPS.

Process

To develop this research, a survey of several local nursery schools in Malaysia was conducted. Out of these, six were randomly picked for the music selection process by JavaScript random number generator. Permission was obtained to visit these nurseries. The selection of the genres of songs was chosen based on two aspects; the teaching syllabus of all six nursery schools, and interviews with the teachers. The genres were first identified from the teaching syllabus and then the different genres of nursery songs were played to the nursery teachers in order to determine which of these were usually used by the teachers as teaching materials in their respective nursery schools. The genres of the children's songs played included rhythm and blues (R&B), western, classical, Malaysian folk songs (Malay and Chinese), and blues. Upon the conclusion of interviews with the nursery teachers, the researcher then played music from all four genres during school activities, curricular, games, and lunch time, with the assistance of the teachers. The children were then asked to vote (identify) for their favourite songs by raising their hands when the songs were played. The researcher shortlisted the top songs with the highest number of votes. A discussion was subsequently held between the researcher and a certified music therapist before the Malaysian folk songs were arranged and recorded. According to the music therapist, infants are naive, simple and innocent (43,44). This means that simple melodies would have better benefits on them than complicated music structures. The simpler the music, the better the results will be in reducing the level of pain in infants (45). Approval from the Research Ethics Committee of UKM was obtained prior to the recruitment of patients to the team conducting the investigation, including the researchers, UKM Medical Centre nurses, and a board certified therapist. Exclusion criteria included infants with neurological diagnoses or syndromes, (e.g. cerebral palsy, hydrocephalus, Rett syndrome) which may suggest an impaired or abnormal pain response, multiple congenital abnormalities that may present difficulties in pain scoring, failed oto-acoustic emissions or automated auditory brainstem response testing on their neonatal hearing screening at birth, infants who were given any analgesics prior to the procedure (e.g. paracetamol, morphine or midazolam), infants with delayed speech and language development for their age as this might affect their hearing. From the criteria set, thirty patients were selected and written informed consent was obtained from the parents. The selected patients were then randomized by using a JavaScript random number generator to produce customized sets of random numbers into either the music listening intervention group or the EMLA group (Figure 3). In the study, the EMLA group was given an application of EMLA which was applied onto the dorsum of the hand over the intended venepuncture site. Application was done in accordance with the manufacturer's instructions. A thick layer of one to two grams was applied under an occlusive dressing 60 minutes prior to the venepuncture (46). In the music group, a placebo cream (Aqueous cream) was applied to the subjects instead of the EMLA cream and the same method was employed for the EMLA group. By using non-invasive pulse oximetry, a baseline monitoring of the patients' heart rates (HR) was obtained, and oxygen saturation (SpO_2) was obtained using a SpO_2 machine 10 minutes before the venepuncture procedure. Headphones were placed onto both groups 5 minutes before the procedure. The music group had music played on the headphones while the EMLA group did not have any music in their headphones. Venepuncture procedures were then carried out as per standard ward protocol. A video recording of the patients was made during the procedure and reviewed independently for the assessment of pain score using the FPS and MBPS by two paediatric registrars i.e. they were blinded to the type of therapy received. The subjects' faces, limbs and postures were exposed during venepuncture so as to allow for the proper assessment of pain scores. In

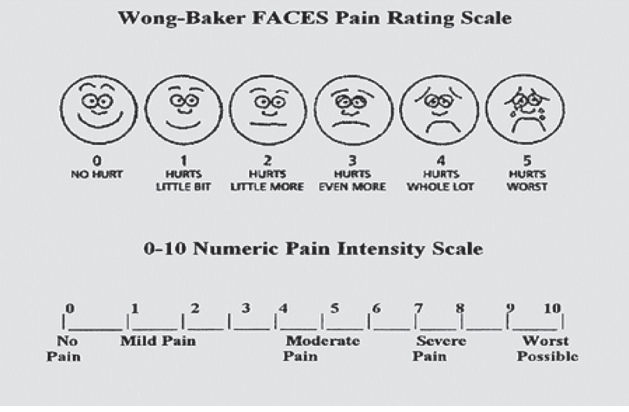

Figure 1. Faces Pain scale (38)

addition to this, the researcher also evaluated the infants' physiological response to pain during the venepuncture procedure by means of HR and pulse oximetry monitoring (SpO_2). During the venepuncture process, the HR, SpO_2 and pain score was documented from baseline i.e. 5 minutes before the start of venepuncture (T=0), first prick (T=1), 2.5 minutes (T=2.5), 5 minutes (T=5) and 7.5 minutes (T=7.5) for every patient. Any number of venepuncture attempts was allowed during the 7.5 minutes. If the venepuncture procedure was unsuccessful and had exceeded 7.5 minutes, the vital signs and pain score were no longer documented. A summary of both parts of the research is shown in Figure 3.

Statistical Analysis

The IBM SPSS (version 22.0) was used for the data analysis of the findings obtained which was used to apply both descriptive (mean, standard deviation and frequency tables) and inferential statistics. The analysis of data involved the mean of 4 parts of the research-the HR, the SpO_2, the FPS, and the MBPS, within the three (3) stages (pre, post and follow-up) between both groups (i.e. experimental and control). Prior to data analysis for quantitative data, normality test was done. Mean comparison for continuous variables between two groups was done using a two-way repeated measure ANOVA followed by Bonferroni test. The significance level in this study was α=0.05 level.

Results

The First Phase of Research-Music Selection

During the song selection process, the majority of nursery children began to perform simple hand gestures while they sang and danced along to the Malaysian folk songs for children. However, when it involved songs in the R&B, western, classical, and blues genres, these were not popular with the children. This is probably because these genres were foreign to them as they were not within their own cultures. On the other hand, Malaysian folk songs have been their companion while growing up, and these songs are easy to comprehend and have simple arrangements. Thus, songs often played such as P. Ramlee's songs and some traditional songs are more favourable to the children (47). In looking at P. Ramlee, it can only be said that as a renowned artiste and song writer, P. Ramlee was a household name that catapulted the growth of Malaysian music and film industry during the 1950's (48). To date, his films and songs are still appreciated by Malaysians of every generation whether young or old.

Observed behavior	Score (0-10)	Operational definitions
Facial expression		
Definite positive expression.	0	Smiling.
Neutral expression.	1	
Slightly negative expression: for example grimace.	2	Brow bulge, naso-labial furrow.
Definite negative expression: i.e. furrowed brows, eyes closed tightly	3	Brow bulge, naso-labial furrow, eyes closed tight, open lips with or without reddened face.
Cry		
Laughing or giggling.	0	
Not crying.	1	
Moaning, quiet vocalizing, gentle or whimpering cry.	2	
Full lunged cry or sobbing.	3	
Full lunged cry, more than baseline cry.	4	To be scored only if infant is crying during baseline.
Movements		
Usual movements/activity, or resting/relaxed.	0	
Partial movement or attempt to avoid pain by withdrawing the limb where the puncture is done.	2	Squirming, arching, limb tensing/clenching.
Agitation with complex movements involving the head, torso or the other limbs, or rigidity.	3	Generalized limb and/or body movements, or rigidity.

Figure 2. Modified Behavioural Pain scale (40)

Some songs have remained a favourite because the melodies are simple. Thus, when the children were approached and asked to sing individually, it was noted that many of the songs they serenaded were mostly Malaysian folk songs for children, which have often been aired on radio and television (49). The children's parents were also interviewed as a way to obtain further insight into the child's music preferences. Most of the parents responded that they preferred to teach their children Malaysian folk songs at home because of the rhythm of the songs, which according to them, is simple and easy to memorize (50). They also claim that their children found it easier to comprehend this type of music as compared to others. This information implies that children who are exposed to Malaysian folk songs for children from an early age continue to learn them throughout their childhood. Based on the information gathered from the nursery teachers and from the responses drawn from the children and their parents, the list below shows the most voted (favourite) songs:

- Terbang Burung Terbang (P. Ramlee)
- Getaran Jiwa (P. Ramlee)
- Adik Manis (P. Ramlee)
- Ni Wa Wa (Luo Zhong)
- Xiao Mi Feng (Wang Shi Quan)
- Shi Shang Zhi You Ma Ma Hao (Lin Guo Xiong)

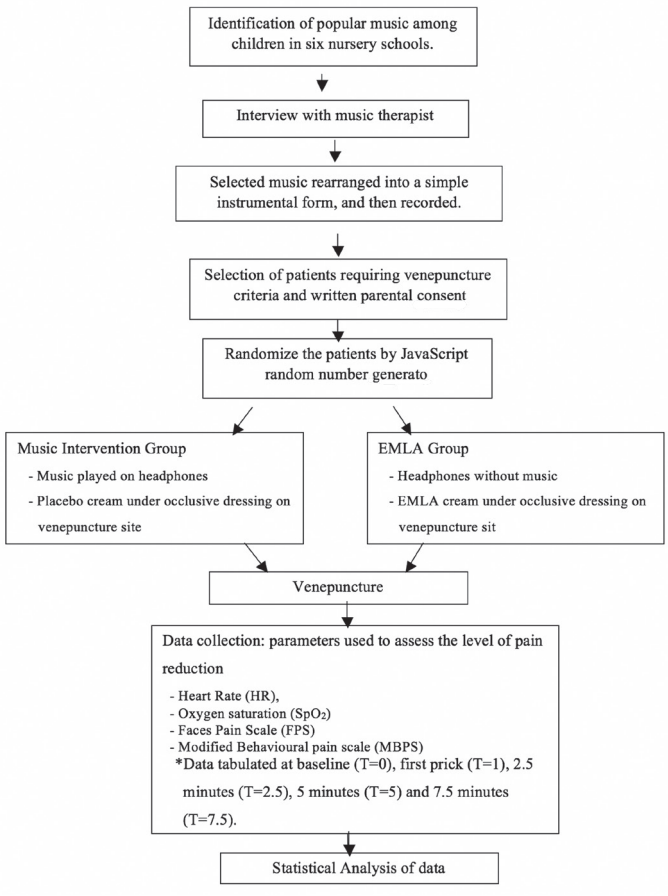

Figure 3. Flow chart of research methodology

All the above songs were used in this research. The melodies of all these songs remained in their original form but the harmonies were rearranged into instrumental form (51). The American Hearing Research Foundation (52) states that pitch higher than 80 decibels is harmful to the human ear. Thus, it is noteworthy that the pitch of the instrumental songs in this research was set at a medium level, which would be more suitable for infants and young children because their physical organs have yet to be fully developed and a high pitch can be harmful to their ears and cause them irritations. One of the criteria set for this study was that the duration of the instrumental music be longer than or equal to the venepucture procedure to ensure that the music is played long enough to distract the infants throughout the procedure so that they would not be anxious or aware of the procedure (53). Simple instrumental music which incorporates piano, percussion and nature sounds is beneficial to mental and physical health (54). In the context of this study, the piano was chosen based on the professional experience of the music therapist who says that children favour sparkling sounds, and the piano is capable of producing orchestra-like sounds with its wide range of 88 keys. Moreover, the piano and percussion are instruments constantly used in the nursery schools making these sounds a familiar one to nursery children. It is theorized that the versatility of the piano in accommodating many styles of music is the most tangible quality in providing the healing effect for people of all ages in music listening intervention. At the New York's Nordoff-Robbins Centre for Music Therapy, the piano is used in helping children and adults to overcome their emotional and physical problems (55). Thus, instrumental songs are played randomly at a continuous pace during the venepuncture procedure.

The Second Phase of Research-Music Listening Intervention

The IBM SPSS Statistics (version 22.0) was used for data analysis. A total of 30 infants were recruited based on their age group and the aforementioned exclusion criteria. The median age of the infants in the music group was 9 months with a median weight of 7.6 kg, while those in the EMLA group had a median age of 8 months and a median weight of 7.5 kg. The analysis of the data involved the mean of 4 parts of the research the HR, the SpO_2, the FPS, and the MBPS, within the three (3) stages (pre, post and follow-up) between both groups (i.e. experimental and control). The sphericity assumption for each part was measured via the Mauchly's test. The differences in the mean of each part were assessed through a two-way repeated measure ANOVA. Prior to data analysis, all variables were subjected to a normality test, and results showed that the data were distributed normally. In the HR section, the sphericity assumption for HR was violated $\chi^2(2)=10.15$, $p=0.006$ therefore, the F-value was adjusted by a Greenhouse-Geisser correction ($\varepsilon=0.76$). The results of repeated measure ANOVA on HR showed that the interaction between the control group and test was not statistically

significant F (1.52, 42.64)=0.4, p=0.62, η^2=0.014. The Post Hoc test (Bonferroni) results in Table I shows that the effect of music listening intervention group was not statistically different from the EMLA group (p>0.05). Similarly, using the Mauchly's test showed that the sphericity assumption for SpO_2 is significant $\chi^2(2)=0.067$, p=0.97 therefore, the F-value was used within Huynh-Feldt estimates of sphericity assumption (ε=1.0). The results of repeated measure ANOVA on SpO_2 showed that the interaction between the group and test was not statistically significant F (2, 56)=2.02, p=0.14, η^2=0.07. The post hoc revealed that the effect of music listening intervention group was not statistically different from the EMLA group (p>0.05), except for the pre-test. In the FPS, the sphericity assumption for this part was significant at $\chi^2(2)=1.78$, p=0.41 therefore, F-value was used within Huynh-Feldt estimates of sphericity assumption (ε=1.0). The results of repeated measure ANOVA on FPS showed that the interaction between the group and test was not statistically significant F (2,56)=1.3, p=0.28, η^2=0.04. However, the effect of music listening intervention group was only statistically different in the post-test. The sphericity assumption for MBPS was significant at $\chi^2(2)=0.4$, p=0.82, therefore, F-value was used with Huynh-Feldt estimates of sphericity assumption (ε=1.0). The results of repeated measure ANOVA on MBPS showed that the interaction between the group and test was not statistically significant F (2,56)=0.12, p=0.9, η^2=0.004. Thus, the effect of music listening intervention group was not statistically different from the EMLA group (p>0.05). The analyses of data T=5 and T=7.5 were omitted in this research as most patients (22 out of 30) completed the venepuncture procedure before 5 minutes. As a result, only the analysis of data T=2.5 is valid for this research. The level of agreement between the two paediatric registrars as reflected by the high Cronbach Alpha scores revealed that their clinical observations and assessments were independent (83.9% to 96.4%), reliable and not influenced by a third party. Based on the above results, music is thus said to have similar effects of EMLA cream in alleviating pain. In other words, music can be used during a venepuncture procedure instead of the EMLA cream. Furthermore, music has many advantages compared to EMLA cream. Firstly, it is of a lower risk and is cost effective as it can be used repeatedly. Secondly, music is readily available and in itself is a form of natural therapy. On the other hand, EMLA cream is time consuming as it has to be applied 60 minutes prior to the procedure. EMLA cream may also incur high expenses as 5 g of EMLA cream costs about RM30 (£5.19) (56). If a doctor fails to locate an infant's blood vessel during the venepuncture procedure after the application of EMLA, reapplication on other intended sites is needed, thereby, incurring additional costs and stress. Furthermore, EMLA cream may also cause short term local blanching effect followed by local erythema. Music as a therapy is better and more suitable for infants for the above reasons (36).

Discussion

This study was a randomised controlled trial study. The results were analysed based on observed behavioural responses by using the two instruments, FPS and MBPS, and through clinical interpretations of vital signs as physiological responses. The results of this research indicate that pain management through the application of EMLA cream or music listening intervention has similar effects in alleviating pain experienced by paediatric subjects who were infants aged between 2 to 24 months old. During the music selection process, nursery teachers and parents were interviewed and the children who were able to comprehend and listen to their preferred choice of music were observed through the layer process as discussed in Figure 3. From the results of the

Table I. Mean difference in heart rate oxygen saturation, Faces Pain scale and Modified Behavioural Pain scale for music and EMLA group

Measures	Time	(I) Music or EMLA group	(J) Music or EMLA group	Mean difference (I-J)	SE	p value
Heart rate	Pre-test	EMLA	Music	11.867	7.069	0.104
	Post-test	EMLA	Music	17.733	9.679	0.078
	Follow up	EMLA	Music	10.467	7.831	0.192
Oxygen saturation	Pre-test	EMLA	Music	2.416*	0.937	0.015
	Post-test	EMLA	Music	1.6	2.242	0.481
	Follow up	EMLA	Music	1.733	2.323	0.462
Faces pain scale	Pre-test	EMLA	Music	0.4	0.559	0.48
	Post-test	EMLA	Music	1.133*	0.53	0.041
	Follow up	EMLA	Music	0.4	0.362	0.278
Modified behavioural pain scale	Pre-test	EMLA	Music	0.933	0.879	0.297
	Post-test	EMLA	Music	1.267	0.924	0.181
	Follow up	EMLA	Music	1.267	0.702	0.082

Based on estimated marginal means, adjustment for multiple comparisons: bonferroni

*: Significant at 0.05 level

observation, Malaysian folk songs for children were more favourable compared to the songs in genres depicting R&B, western, classical, and blues amongst children in Malaysian nurseries. The former was preferred over the latter choices possibly due to cultural differences. It may also be attributed to the fact that Malaysian children have been exposed to these songs so often that these have become their constant companion whilst growing up (57). Consequently, these songs are more familiar to them and it makes it easier for them to understand (58). This study has shown that there was no statistical significance between the EMLA cream, and music listening intervention group, thereby; both forms of interventions are comparable. The elevated HR and SpO_2 indicate that the subjects were anxious and in pain during the venepuncture procedure. An increase in the patient's HR and SpO_2 indicate that the moods of the patients are at stress levels. The results of this research showed that a patient's HR and SpO_2 in the music listening intervention group can be lowered to a comparably similar rate as that of the EMLA group by merely using non-invasive music therapy. The p-value for the HR and SpO_2 is more than 0.05, there by, proving that music has a similar effect to EMLA in decreasing the pain level.

Observations conducted in this research began from the moment the patients were prepared for the venepuncture procedure. The HR of the patients aged between 1 to 2 years old increased as they entered the procedure room. Their baseline resting HR was between 80 to 130 beats per minute but this increased to beyond 130 beats per minutes there after, which showed that as age increases, the awareness of surrounding also increases. Doctors allowed the patients' mothers to enter the procedure room to provide comfort to the child. Based on our observations, it was noted that the patients became calmer upon hearing their mothers' voices (59). The patients' being able to recognise their mothers' voices, indicates that they may also recognise the music frequently played at home (60). It is possible that playing this music during the venepuncture process will provide better distraction for the infants, thus providing better comfort. Based on our observation, the patients appeared to be anxious due to the unfamiliar environment they were in as well as the medical procedure itself. It was interesting to note that all the patients started to cry as they entered the procedure room. However, four patients in the music listening intervention group stopped crying when the music began to play; proof that music successfully diverted their attention, reducing the level of pain experienced (61). One of the biggest problems encountered during the research was the different levels of pain tolerance between the patients (62). It was noted that some patients under one year old did not realise that they had entered the procedure room, hence, they were neither nervous nor stressed. On the other hand, some patients aged between 1 to 2 years old got extremely nervous and stressed the moment they entered the procedure room, and this affected the baseline data collection. Two patients also became more nervous and anxious after listening to the music because they started crying and their HR increased. In order to obtain more accurate results, a baseline reading of the patients who were induced into a relaxed state before the venepuncture procedure should be acquired. Results, however, showed that the children aged one year old and younger appeared to benefit more from the music than the older ones. According to Oehler (as cited in 37), this is because distraction among older children who are cognitively more advanced is different from the distraction experienced by infants. Some of the parents were intrigued when it was explained to them how music listening intervention would help their children during the venepuncture procedure as they were very new to this concept. After listening to the explanation, most of the parents consented and agreed to participate in the research. However, there were also parents who refused to give permission, fearing untoward effects on their children. This impact could be interpreted in many ways, one of which suggests that music listening intervention is new and peculiar to them, thus they were not receptive. Another factor which affected the venepuncture procedure was the patient's familiarity towards the songs (63). Several patients from the music group enjoyed the music once it was played. One patient even danced along to the music. Fifty percent of the parents requested that the patients' favourite music be played. It is possible that the provision of music videos for patients in the music listening intervention sessions may produce an even greater decrease in the pain levels experienced by the patients during a venepuncture procedure because music videos are visually attractive compared to music alone. According to Valkenburg and Vroone (64), young children's attention to television is determined by the auditory, visual, and content features of the programme and by programme difficulty. Their results showed that among infants, salient auditory and visual features (e.g. applause, visual surprises) particularly attract their attention. Results also suggest that history of previous venous cannulation may also affect the patient's response in the procedure. If the patient's blood vessels are fine and difficult to locate, this can result several attempts to administer venepuncture procedures (65). This means that the patient would have to endure more pain, and consequently develop a bad recollection of the procedure. In this research, it was noted that almost half of the patients had had to go through more than one attempt, and it appears that the calming effect of the music is less effective if the patient is already fearful of the procedure. The age of the patients may also be another factor contributing to the effectiveness of music in alleviating pain. The younger the patient the more effective the music is (66). Patients who have yet to develop bad experiences related to the venepuncture procedure were easily calmed by the music as they were unaware of the procedure. It appears that the patients aged over one year old would already know of the venepuncture procedure and thus, be more likely to be aware of the pain. The environment of the procedure room is also another factor affecting the impact of music listening intervention in pain management (67). When patients were

brought into the procedure room, they were already aware of what they were about to experience. Some of the patients started to cry and struggle even before the procedure. This caused an increase in their HRs. Their reaction resulted in difficulty in getting them to put the headphones on. This situation may have been avoidable if music were played to them before they entered the procedure room. Although EMLA cream may be the first choice of the doctors when addressing paediatric pain management, it is not used in all hospitals because it requires time to take effect. It has to be applied 60 minutes prior to the venepuncture procedure (68). Therefore, under emergency circumstances doctors prefer not to apply EMLA cream. Usually, blood sampling is required immediately for rapid results. Moreover, during the waiting period, patients may smear or remove the EMLA cream from the intended site and this is dangerous as they may consume the cream in view of their developmental age. The EMLA cream will also lose its effect once the occlusive dressing falls off, thus if a doctor fails to locate a patient's blood vessel at the first attempt, he/she would have to reapply the EMLA cream and wait for another 60 minutes. This consumes time, energy and is costly. Based on our study, music listening intervention has a positive effect on infants' venepuncture experience. Results of this study reflect that the use of music in pain management alleviates the pain levels experienced by hospitalized infants and this finding is comparable to EMLA which has been regarded as a clinical gold standard.

Study Limitations

This preliminary research is restricted to the use of music in a medical procedure involving only venepuncture. The possibilities for future research focusing on various aspects of music listening intervention and the factors affecting the effectiveness of pain management are vast and challenging. Further research may be able to identify other ways that can improve pain management in paediatrics for selected clinical procedures and rehabilitation purposes.

Conclusion

When dealing with medication on children, it is important to keep in mind the stage of their physical and developmental growth as well as their maturity level and emotional development. There are various paediatric surgery and medical procedures and therapeutic interventions; venepuncture and venous cannulation are some of the common medical procedures performed on infants (69). It is important to realize that no matter how mature the child appears, he/she still needs to be treated differently from adults (70). This aspect of "child friendly" procedure is especially important amongst chronic paediatric patients. Needles and pain are one of their biggest fears and inappropriate pain management during medical procedures may cause long term pernicious effects (71). Furthermore, it is crucial to take into account the children's interest in music based on their culture, background and age (72). Results of this research show that children prefer simple, interesting and cheerful music, and this is evidenced by the musical interest of Malaysian children in the Malaysian folk songs for children used in this research. Although music listening intervention may still be a very new concept in Malaysia (73), compared to other therapies or medical treatment, it is a natural way of reducing pain as it does not use any form of medication. Music is low in cost, readily available and has no untoward side effects, thus medical practitioners should support, encourage and promote the benefits of music listening intervention. In addition, it is recommended that the medical professionals work together with rehabilitative personnel and music therapists in the development and advancement of music listening intervention in Malaysia since it is a safe method that can be used to assist children in alleviating pain both physically and mentally in a natural way. Pain is a common issue in paediatrics. Inappropriate pain management during medical procedures may cause long-term detrimental effects that may affect the child's development. These are especially true for infants who are admitted to hospitals and have to undergo many medical procedures, medications, physical and mental exhaustion in an unfamiliar environment. Poor management may result in the child having a phobia towards seeking treatment at the hospital (11). Music is useful as an agent which induces relaxation and reduces anxiety and pain. When played, music can also divert the patient's attention from pain (74). This is the basis of music listening intervention in pain management programs.

Ethics

Ethics Committee Approval: This study was approved by the Research Ethics Committee of University Kebangsaan Malaysia (approval number: FF-264-2011)

Informed Consent: Consent was filled out and given by the parents and guardians of the participants.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.A.L., W.J.T., Concept: W.F.B., M.N.H., Design: W.F.B., M.N.H., Data Collection or Processing: W.F.B., W.J.T., Analysis or Interpretation: W.F.B., Literature Search: W.F.B., Writing: W.F.B.

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Original Article

Varicella-Related Hospitalizations Among Immunocompetent and Immunocompromised Children in Pre-Vaccine Era: A Tertiary Care Center Experience in Turkey

Özlem Akgün Doğan, Seda Topçu, Naciye Gönül Tanır

University of Health and Sciences, Dr. Sami Ulus Maternity and Children's Training and Research Hospital, Clinic of Pediatrics, Ankara, Turkey

ABSTRACT

Aim: Although varicella is a common, contagious, self-limited childhood disease, it can cause significant long-term sequelae and mortality in both immunocompetent and immunocompromised children. The aim of the present study is to identify and review varicella-related hospitalizations, admissions and complications of primary varicella infection among immunocompetent and immunocompromised children of a large unselected local population in a governmental institution.

Materials and Methods: Demographic aspects, clinical features, microbiological findings, complications, managements and outcome of the patients hospitalized for varicella were analyzed retrospectively.

Results: Among 100 such children, 66 were immunocompetent and 34 were immunocompromised. Secondary bacterial infection was the most common complication in both groups. The second most common complication in the immunocompetent group was neurological complications (21%) followed by varicella-zoster virus (VZV) pneumonia (2%). In the immunocompromised group neurological complications and VZV pneumonia were not observed. Hematological complications were seen in 5% of the immunocompetent patients and 6% of the immunocompromised patients. Mortality was seen in 2% in the study group, one patient in the immunocompetent and one in the immunocompromised group.

Conclusion: Despite a common perception of varicella infection being highly contagious but harmless, complications requiring hospitalization are frequent, potentially serious and costly even in healthy children. Since varicella virus vaccine prevents most of the morbidity and mortality caused by primary varicella in children, prevention rather than the treatment will be the optimal approach.

Keywords: Varicella, complication, healthy, immunocompromised, child

Introduction

Varicella is a common, contagious disease caused by primary varicella-zoster virus (VZV) infection, and it is usually a benign and self-limited childhood disease in healthy children (1,2). The disease course is usually more severe in immunocompromised children. However, most hospitalizations for varicella are of previously healthy children. Varicella can cause significant long-term sequelae and mortality in both immunocompetent and immunocompromised children (1,3). The American Academy of Pediatrics and Advisory Committee on Immunization recommends varicella vaccine to prevent most of the morbidity caused by primary varicella in children. Universal vaccination in the United States since 1995 has substantially reduced the incidence of varicella, hospital admissions, and deaths. In Turkey, routine varicella vaccination is being performed since 2013 as a single dose at 12 months of age. Data on severe complications of varicella

Address for Correspondence
Özlem Akgün Doğan MD, University of Health and Sciences, Dr. Sami Ulus Maternity and Children's Hospital, Department of Pediatrics, Ankara, Turkey
Phone: +90 505 640 78 47 E-mail: ozlem.akgun@hacettepe.edu.tr ORCID ID: orcid.org/0000-0002-8310-4053
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in children in pre-vaccine period is valuable and essential for a comparison between pre- and post-vaccination period to develop immunization recommendation strategies. The aim of the present study is to identify and review varicella-related hospitalizations, admissions, and complications of primary varicella infection among immunocompetent and immunocompromised children of a large unselected local population in an institution in pre-vaccine period, in Ankara, Turkey.

Materials and Methods

This study was conducted as a retrospective cohort study at a tertiary care reference center for children with a total number of 270.000 clinic patients per year. Data from children hospitalized with a diagnosis of varicella between January 2004 and December 2010 were analyzed for clinical features, immune status, microbiological findings, varicella complications, management, and outcome.

VZV infections were diagnosed based on typical skin findings, including generalized papullar and vesicular rashes at different stages. The children were included in the study if VZV infection required hospitalization, whether for a varicella-related complication or for immunosuppression. They were classified into two groups as immunocompromised and immunocompetent. An immune compromising condition was defined as any congenital or acquired immunodeficiency, malignancy, receipt of high dose corticosteroids or chemotherapy within 30 days before the onset of varicella, and severe malnutrition. The term varicella-related complication was applied to all varicella associated events and classified into five groups; secondary bacterial infections, VZV pneumonia, neurological, hematological and other (hepatitis, pancreatitis, stomatitis, disseminated varicella infection). The diagnosis of bacterial superinfection was established by clinical/laboratory findings or was confirmed by bacterial cultures. VZV pneumonia was defined as fever, dyspnea, cyanosis, chest pain and radiographic findings occurring within 2-6 days of the onset of varicella. Neurological complications were diagnosed if fever, altered level of consciousness, ataxia, nuchal rigidity along with consistent cerebrospinal fluid (CSF) or electroencephalogram findings were present. Thrombocytopenia meant a platelet count below 100.000 cells/mm^3 and leukopenia as white blood cell count below 4.000 cells/mm^3. Coagulation disorders were defined as prolonged prothrombin time, activated partial thromboplastin time and consistent variations in d-dimer and fibrinogen levels. Hepatitis was defined as the elevation of serum alanine aminotransferase and aspartate aminotransferase levels to at least twice the normal amount. Disseminated varicella meant laboratory and clinical findings representing infectious involvement in at least two parenchymal organs. Pancreatitis was established by elevated amylase levels, clinical and ultrasonography findings. Stomatitis was defined as painful flat-based ulcers in oral mucosa that cause difficulty in eating. Newborns and children older than 12 years were accepted as high-risk groups for severe VZV infection (1,4).

University of Health Sciences, Ankara Keçiören Training and Research Hospital Ethical Committee (approval number: 1300). In this study, data were obtained from file records, and consent was not obtained due to the retrospective nature of the study.

Statistical Analysis

Statistical analysis was performed via SPSS 16.0 program. Collected data was presented as the average and standard deviation for symmetrically distributed data and as the mean value for non-symmetrical data. Categorical data (sex, complication, etc.) were presented as incidence. Differences were considered significant at a value of $p<0.05$.

Results

Between January 2004 and December 2010, 1000 children were referred to the hospital with the diagnosis of varicella and 100 were hospitalized. Of those, 66 were previously healthy, 34 had chronic illnesses leading to immunosuppression. Of the 34 patients, 21 were hospitalized for antiviral therapy despite the absence of complications. All of the immunocompetent patients were hospitalized for complications. None of the children had been previously immunized against varicella. Demographic characteristics and length of hospital stay are summarized in Table I.

Immunocompetent Patients

In 66 patients there were 85 complications, with fourteen patients (21%) having multiple complications. Distribution of the complications is summarized in Table II. Among secondary bacterial infections, the most common complication was skin/soft tissue infection. Soft tissue infections were mainly seen as invasive bacterial infections (18 patients). *Staphylococcus aureus (S. aureus)* was isolated from superficial infection

Table I. Demographic features of the immunocompetent and immunocompromised groups

	Immunocompetent patients	Immunocompromised patients	Total
Number of patients	66	34	100
Gender (F/M)	26/40	16/18	
Age groups			
0-1 years	27	4	31
1-4 years	22	12	34
4-9 years	12	13	25
9-12 years	3	3	6
>12 years	2	2	4
Mean duration of hospital stay (days)	7.7 (median: 7)	6.6 (median: 7)	7.3 (median: 7)

F: Female, M: Male

sites in two separate patients with cellulitis and skin abscess. Group A beta-hemolytic streptococcus (GABHS) was isolated in pus culture in one patient with skin abscess, and in a single case of necrotizing fasciitis. Secondary bacterial pneumonia was the second complication in the secondary bacterial infection group; viridans streptococci and coagulase-negative staphylococcus were the isolated pathogens. Hospitalization due to secondary bacterial infection was most common in the 0-1 age group (24 patients). The second largest group covered neurological complications. Acute cerebellar ataxia was the most common complication followed by cerebellitis. Abnormal electroencephalogram with diffuse slowing was found in one patient with encephalitis. Ten patients underwent CSF examinations and 2 had increased cell counts with normal protein and glucose levels. No pathogens were isolated from CSF examination cultures in any of the cases. All patients with neurological complications were discharged without major sequelae. Reye syndrome was not reported. Neurological complications mostly affected the 1-4 age group (7 patients). VZV pneumonia was diagnosed in 2 patients, one was seven months old and the other was 11 years old. Neither of them had any risk factors for severe VZV

Table II. Type and frequency of complications and laboratory values in the immunocompetent and immunocompromized groups

	Immunocompetent patients						**Immunocompromised patients**					
Complications	**n (%)**	**Age (mean) (years)**	**Mean**				**n (%)**	**Age (mean) (years)**	**Mean**			
			Duration of hospital stay (days)	**WBC (1000 cells/ mm³)**	**CRP (mg/ dL)**	**ESR (mm/ hr)**			**Duration of hospital stay (days)**	**WBC (1000 cells /mm³)**	**CRP (mg/ dL)**	**ESR (mm/ hr)**
Secondary bacterial infection	46 (54)	2.4 (median: 1.2)	8.1 (median: 6.5)	11.1	67.4	48.3	8 (50)	4.6 (median: 3)				
Cellulitis	18						3					
Pneumonia	16						4					
Skin abcess	3						-					
Preceptal cellulitis	3						-					
Impetigo	3						1					
Arthritis	1						-					
Conjunctivitis	1						-					
Necrotizing fasciitis	1						-					
VZV pneumonia	2 (3)	5.8	12	12	190	56	0	-	-	-	-	-
Neurological complications	18 (21)	4.9 (median: 3.5)	7.6 (median: 7)	9.8	17.3	47.4	0	-	-	-	-	-
Ataxia	5						-					
Cerebellitis	4						-					
Febrile seizures	3						-					
Encephalitis	3						-					
Meningitis	2						-					
Facial paralysis	1						-					
Haematological complications	4 (5)	5.5 (median: 5)	9.8 (median: 7.5)	9.1	98.7	41.7	1 (6)	12	2	6.4	10	8
Thrombocytopenia	2						-					
Granulocytopenia	1						-					
DIC	1						1					
Other complications	15 (18)	2.8 (median: 0.6)	8.3 (median: 6)	8.8	64.6	39	7 (44)	6.2 (median: 7)	6.1 (median: 6)	18.2	14.1	19.1
Hepatitis	10						6					
Disseminated varicella infection	2						1					
Stomatitis	2						-					
Pancreatitis	1						-					

N: Number, DIC: Disseminated intravascular coagulation, WBC: White blood cell, CRP: C-reactive protein, ESR: Eritrocyte sedimentation rate, VZV: Varicella-zoster virus

infection. No pathogens were isolated from blood cultures in either of the patients. Hematological complications were seen in 4 patients. Of these, 2 had thrombocytopenia, 1 had granulocytopenia and 1 had disseminated intravascular coagulation (DIC). Two of them were in the 0-1 age group, and the other 2 were in the 9-12 age group. One of the patients that developed thrombocytopenia was a 10-years-old male patient, admitted to the physician for epistaxis and skin bruising. In the complete blood count, platelet number was 2000 cells/mm^3 and in the bone marrow aspiration, increased number of megakaryocytes were seen, suggesting the diagnosis of immune thrombocytopenic purpura (ITP). Disseminated varicella was seen in 2 female patients aged 7 months and 11 years, and neither of them had risk factors for a severe disease. Overall, 38 of the patients (58%) received antibiotics and acyclovir, 17 (26%) received only antibiotics, 9 (14%) only acyclovir, and 2 (3%) received neither of these. Two patients received intravenous immunoglobulin (IVIG), one with disseminated varicella and necrotizing fasciitis, and the other with ITP. The patient with necrotizing fasciitis required surgical intervention for debridement. This patient with dermal scarring was the only patient who had sequelae attributable to varicella complications. The only fatal outcome was a 2-months-old patient who had experienced household exposure to varicella three weeks before the appearance of the rash. She was admitted to the hospital on the 10^{th} day of the rash with fever, feeding difficulty and tachypnea. Diffuse pulmonary infiltrations were detected in the chest X-ray. Despite the intravenous antiviral and antibacterial therapy, she died due to respiratory failure on the fourth day of hospitalization.

Immunocompromised Patients

Patients in the immunocompromised group, with or without complications, were hospitalized for antiviral therapy and observation. Immune-compromising conditions were chemotherapy within 30 days before the onset of varicella in 27 patients, high-dose corticosteroid therapy within 30 days in 4 patients (two with Nephrotic syndrome, one with membranoproliferative glomerulonephritis, one with acute rheumatic fever (ARF), and congenital immunodeficiency in two patients (one with Whim syndrome, one with common variable immunodeficiency), and severe malnutrition in one patient. In 34 patients there were 16 complications, and two of them had more than one complication. Distribution of the complications is summarized in Table II. Among the patients with multiple complications, one had cellulitis and hepatitis, and the other had DIC, hepatitis, and disseminated varicella. Overall, 18 (53%) of the patients received only acyclovir, 16 (46%) received both antibiotics and acyclovir. Two patients with congenital immunodeficiency received IVIG. Both of the patients had been receiving regular IVIG before the VZV infection. Neither of the patients required surgical intervention. Major sequelae were not recorded. The only fatal outcome was a 12 year-old-female who was receiving high dose steroids for ARF. She was admitted to the hospital two days after the onset of rash with generalized hemorrhagic vesicles, hematuria, and arthralgia. She developed thrombocytopenia, DIC, and fulminant hepatic failure on the third day of hospitalization and died due to disseminated varicella despite aggressive therapy.

Discussion

Although varicella is known as a benign disease of childhood, hospitalization rates have been reported to be 2-3/1000 among children (2). In Turkey, it is anticipated that 90% of the children will be exposed to the disease until the age of 15 and the estimated hospitalization rate in the prevaccine period was reported to be 5.29-6.89/100.000 (5). Our study was conducted at a tertiary care center with a number of 270.000 clinic patients per year, and among 1000 varicella related admissions, 100 varicella-related hospitalizations were determined. We found that 10% of the varicella-related admissions ended up being hospitalized. The high hospitalization rate in our study could be attributed to the fact that our study was conducted in a tertiary center to which complicated and severe cases are referred.

Varicella has the highest incidence in children aged 1-9 years. The highest hospitalization rates are reported during the first year of life, which has also been observed in the immunocompetent group in our study (1,4,5). Population-wide vaccination and herd immunity is the only realistic option for the prevention of the disease in children under 1 year old. The distribution of the complications was consistent with previous studies (6-9). Secondary bacterial infections caused by particularly GABHS and *S. aureus* are the most common complications (1,3,7). Consistently in our study, secondary bacterial infections were most common; *S. aureus* being isolated in 2 separate patients with cellulitis and skin abscess; GABHS in 2 separate patients with skin abscess and necrotizing fasciitis. Neurological complications, which are very worrisome for caregivers, are second in order of frequency among varicella-associated complications, especially in previously healthy children younger than 5 years of age (1,3,6-9). VZV pneumonia is a well-recognized serious complication of varicella, especially in immunocompromised children, adults and newborns. However, it is rare among previously healthy children. In our study, although neurological complications were also seen second in order of frequency, and mostly affected the 1-4 age group among the immunocompetents, they were not seen in the immunocompromised group. Like neurological complications, VZV pneumonia was not detected in the immunocompromised group. These findings may be related to the small study population but can also be explained by the heightened risk awareness of the caregivers of these patients, and the early initiation of antiviral treatments. In our study, VZV pneumonia was seen in 2 (3%) patients in the immunocompetent group and neither of them had any of the risk factors.

Thrombocytopenia, DIC and purpura fulminans are the well-known hematological complications of varicella although they are rare in childhood (3,7,9). In our study hematological complication rate was found as 5% in the immunocompetent group and 6% in the immunocompromised group consistent with previous studies (3,7,10). Factor V Leiden, protein C and S deficiencies were suggested as risk factors for DIC in VZV infection (11,12). However, in our study it was not possible to make an interpretation because such hypercoagulability factors were not studied in patients with DIC. Varicella-related ITP was reported in studies from Sweden and Israel only in two previously healthy children (5,13). This rare complication was also seen in our study in the immunocompetent group with a recovery period of six months. Varicella appears to cause transient hepatitis in children with a rate of 3-3.5% (3,7,14). In our study the overall hepatitis rate was 16% with 6 (9%) patients in the immunocompetent and 10 (29%) in the immunocompromised group. None of the patients developed hepatic failure except one patient with disseminated varicella infection. The high rate of hepatitis in the immunocompromised group may have been due to the manifestations of the underlying disease. Myocarditis, pericarditis, pancreatitis, renal complications, and Reye syndrome are very rare complications of varicella. In our cohort, there was only one case of pancreatitis. Reye syndrome was not observed, possibly owing to the withholding of salicylates from children since the 1990's. Disseminated varicella is a severe complication of varicella with visceral organ involvement, severe hemorrhage, and coagulopathy. Although adolescents, adults, pregnant women, newborns, immunocompromised children are at increased risk of disseminated varicella, previously healthy children may also be affected with high morbidity and mortality rates. In studies from Turkey and Sweden disseminated varicella was seen in 3% of previously healthy children, which is consistent with our study, suggesting that varicella may also be severe in previously healthy children (6,8). In our study, the median hospital stay length was 7 days similar to previous studies in other countries which reported median hospital stay as ranging from 4 to 7 days (6,7). Only one patient had long-term sequelae, attributed to necrotizing fasciitis in previously healthy children, consistent with a study from Germany which reported the sequelae rate as 1.7% (15). Two patients (2%) died, one of secondary bacterial pneumonia and the other of disseminated varicella. In studies from Ireland and England, the death rate was found as 3.1% and the high rate was attributed to the involvement of only severe cases in that study (16). In other studies from Sweden and Germany, no fatality was reported (9,10). Although varicella usually results in mild to moderate illness in immunocompetent patients, serious complications can arise (1). Most of the varicella-related complications were reported in children without severe underlying immune compromising conditions (14,17,18). Our study suggests that in previously healthy children, severe complications requiring hospitalization are more than in the immunocompromised children due to the increased risk awareness and early initiation of antiviral treatment in these children.

Study Limitations

This study was conducted in a small group of patients in a single center thus has limitations for generalisation of the data.

Conclusion

In conclusion, since varicella virus vaccine prevents most of the morbidity and mortality caused by primary varicella in children, prevention rather than the treatment has therefore been recommended as the optimal approach (2,19,20). Universal vaccination appears to be the best way to reduce the incidence of varicella, and achieving this will also protect those who are not eligible for vaccination such as immunocompromised individuals and infants (19,21). Despite the common perception of varicella infection being harmless, complications requiring hospitalization are frequent, potentially serious, and costly even in healthy children. All of the immunocompetent patients in the study group, who needed hospitalization for varicella-related complications had serious medical conditions. Universal varicella immunization that was launched in 2013 may reduce this high rate of varicella-related complications and hospital admissions in our country. The surveillance of varicella-associated complications is essential for monitoring the impact of varicella immunization. Our study provides data to compare hospitalization indications and varicella complications in immunocompromised and immunocompetent children.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences, Ankara Keçiören Training and Research Hospital Ethical Committee (approval number: 1300).

Informed Consent: In this study, data were obtained from file records, and consent was not obtained due to the retrospective nature of the study.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.G.T., Ö.A.D., S.T.O., Concept: N.G.T., Ö.A.D., Design: N.G.T., Ö.A.D., Data Collection or Processing: Ö.A.D., S.T.O., Analysis or Interpretation: N.G.T., Ö.A.D., Literature Search: Ö.A.D., S.T.O., Writing: Ö.A.D.

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Original Article

The Surgical Management Strategies in Congenital Pulmonary Airway Malformations: According to the Location of the Pulmonary Involvement

Emre Divarcı, Bade Toker, Zafer Dökümcü, Coşkun Özcan, Ata Erdener

Ege University Faculty of Medicine, Department of Pediatric Surgery, İzmir, Turkey

ABSTRACT

Aim: Treatment of congenital pulmonary airway malformations (CPAMs) consists of different surgical options. In this study, we aimed to report our surgical management strategy according to the location of pulmonary involvement.

Materials and Methods: We retrospectively analyzed the medical records of patients who underwent surgery for CPAMs between 2005 and 2015. The data including patient demographics, pre-operative clinical features, surgical management strategies and postoperative results were reviewed.

Results: Twenty patients (14 male, 6 female) with a median age of 4 months (1 day-12 years) were operated on. Antenatal diagnosis was positive in 12 patients (60%). The other patients were admitted with a median age of 3.5 years (1 day-12 years). Respiratory infection was seen in four patients (20%). Nine patients underwent early operation due to severe dyspnea and recurrent respiratory infection (45%). Lobectomy was performed on 17 patients with single lobe involvement (85%). Lobectomy for major lesion and segmentectomy for minor lesion was performed on two patients with unilateral multi-lobar involvement. One patient with bilateral multi-lobar involvement required multiple thoracoscopic wedge resections. Two patients who had severe dyspnea before surgery required mechanical ventilation after the operation, and one of them died. Two postoperative complications, empyema and pneumothorax were seen. Mean postoperative follow-up period was 5.5 years.

Conclusion: CPAMs must be excised totally due to the risk of pulmonary infection and malignancy. The resection strategy should be decided according to the number of the affected lobes. Lobectomy should be performed in single lobar involvement. Unilateral multi-lobar involvement requires lobectomy for a major lesion and segmentectomy for a minor one. Thoracoscopic multiple wedge resections should be the option in bilateral multi-lobar CPAMs.

Keywords: Congenital pulmonary airway malformation, congenital cystic adenomatoid malformation, lung cyst, children

Introduction

Congenital cystic adenomatoid malformations (CCAMs) are congenital lung malformations derived from a hamartomatous lesion of the bronchial tree (1). These lesions account for approximately 95% of congenital cystic lung diseases (2). In recent years the name of this clinical entity was changed to congenital pulmonary airway malformations (CPAMs). This new name has gained popularity and is primarily preferred in the current medical literature (3). The course of these lesions could be varied in a broad clinical spectrum as hydrops and fetal death due to rapid growing, or being asymptomatic without clinical problems (4,5). Recurrent pulmonary infections, pnemumotorax and primary lung malignancies are the potential clinical problems which could be seen in the postnatal period (6,7). Pulmonary blastoma, rabdomyosarcoma, bronchogenic carcinoma and various sarcomas were reported in the literature which got derived from CPAMs (8-11). Therefore, surgical resection is usually suggested to avoid these potential devastating clinical problems. Lobectomy is usually preferred in the surgical treatment of CPAMs in order to avoid leaving

Address for Correspondence
Emre Divarcı MD, Ege University Faculty of Medicine, Department of Pediatric Surgery, İzmir, Turkey
Phone: +90 535 726 87 63 E-mail: emre.divarci@ege.edu.tr ORCID ID: orcid.org/0000-0002-8519-8794
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residual disease in the remaining lobe (3). However, the management of CPAMs could be a big challenge in patients with multilobar involvement. Formal lobectomies could result with pneumonectomy in these patients (12). In this study, we aimed to present our surgical management strategies in CPAMs according to the different locations of the pulmonary involvement.

Materials and Methods

The medical records of patients who underwent surgery for CPAMs between 2005 and 2015 were retrospectively analyzed. Data including age, time of clinical admission, respiratory problems, surgical resection strategies according to anatomic locations of the cystic lesions and postoperative complications were reviewed. The time of surgical resection was postnatal 1 to 6 months old in patients with antenatal diagnosis of CPAMs. However, early surgery was required in some of these patients in the early postnatal period due to severe respiratory defficiency. The other patients who were admitted after infancy period underwent elective surgical excision without any delay. The main surgical approach was thoracotomy. Thoracoscopy was preferred in only one patient with bilateral multi-lobar involvement. The surgical strategy was decided according to the anatomic location of the pulmonary involvement;

- Single lobar involvement: Lobectomy.
- Unilateral multi-lobar involvement: Lobectomy to the major lesion, segmentectomy to the minor.
- Bilateral multi-lobar involvement: Thoracoscopic wedge resections in multiple sessions.

All of the parents gave their informed consent prior to their inclusion in the study.

Results

Twenty patients (14 male, 6 female) with a median age of 4 months (range: 1 day-12 years) were operated on. The time of clinical admission was early postnatal period for 12 patients who had antenatal diagnosis (60%). The other eight patients who had not had antenatal diagnosis were admitted with a median age of 3.5 years (range: 1 day-12 years). Main results are summarized in Table I. Pre-operative respiratory infection was seen in four patients (20%). Nine patients underwent early operation due to severe dyspnea and recurrent respiratory infection (45%). All of the patients were examined by computerized tomography after neonatal period as a routine pre-operative work-up. The most frequent location for pulmonary involvement was left lower lobe (40%). The other locations were left upper lobe (20%), right middle lobe (15%), right upper lobe (10%), unilateral multilobar (10%), bilateral multilobar involvement (5%) (Figure 1). Operative strategy was decided according to the location of the pulmonary involvement of the cystic lesions. Lobectomy was performed on 17 patients with single lobar involvement (85%). Lobectomy to major cystic lesion and segmentectomy to minor lesion was performed in two patients with unilateral multi-lobar involvement (10%). One patient with bilateral multi-lobar involvement required multiple thoracoscopic wedge resections (5%) (Figure 2). Two patients who had severe dyspnea before surgery required mechanical ventilation after the operation. Mortality was seen in one of these patients due to severe respiratory insufficiency (5%). Empyema and pneumothorax were two postoperative early complications which were treated succesfully. Recurrence, infection or malignancy was not observed in any of the

Table I. The data of patient demographics and clinical features of overall group

Number of patients	20 patients (14 M, 6 F)
Median age of operation	4 months (1 day-12 years)
Antenatal diagnosis	60% (12 patients)
Median admission age of patients without antenatal diagnosis	3.5 years (1 day-12 years)
Clinical presentations	
Asymptomatic (n=8) Dyspnea (n=6) Respiratory infections (n=4)	40% 30% 20%
Early operation due to severe dyspnea and recurrent respiratory infection	45% (9 patients)
Operative strategy	
Single lobar involvement (n=17)	Lobectomy
Unilateral multi-lobar involvement (n=2)	Major lesion: Lobectomy Minor lesion: Segmentectomy
Bilateral multi-lobar involvement (n=1)	Thoracoscopic wedge resections in multiple sessions

F: Female, M: Male

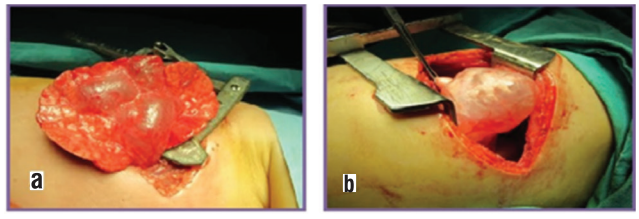

Figure 1. a) The lesion was identified in the right middle lobe and exteriorized through the thoracotomy incision. b) A huge cystic lesion was detected in the left upper lobe

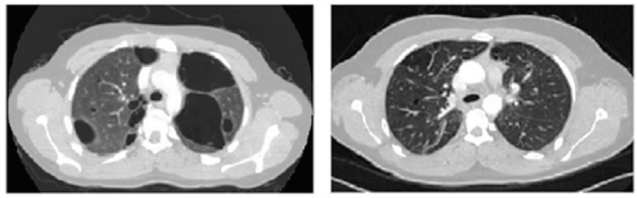

Figure 2. Pre-operative and postoperative computed tomography scans of a patient with bilateral multi-lobar pulmonary involvement of cystic lesions
CT: Computed tomography

patients during follow-up. Mean postoperative follow-up period was 5.5 years.

Discussion

The management strategies in CPAMs are usually based on potential detrimental clinical problems as recurrent pulmonary infections and rarely malignancy. A case was also reported from our clinic in recent years with primary pulmonary rhabdomyosarcoma arising within cystic adenomatoid malformation (11). Lobectomy is the most commonly preferred surgical technique to resect all of the cystic lesions to avoid residual disease. In recent years, non-operative management with clinical follow-up has begun to be advocated in some of the centers due to the frequently benign asymptomatic course of these lesions (13,14). However, the follow-up strategy is not clear. The interval periods between the radiological imaging studies and the type of the imaging modalities as computerized tomograghy or chest X-ray in the follow-up are not clearly defined in the literature, nor is the management strategy in patients with multi-lobar pulmonary involvement (12). Surgical excision is usually suggested to avoid potential clinical problems. Kapralik et al. (15) reported a systematic review and meta-analysis to discuss surgical versus conservative management of CPAMs in children. They suggested elective resection of asymptomatic lesions to avoid development of symptoms. Optimal age for surgery was not clearly defined in the reported studies. Naito et al. (16) reported that earlier lobectomy did not effect the pulmonary functions in the long-term. Sullivan et al. (17) discussed the optimal age for elective surgical resection for asymptomatic CPAMs with meta-analysis. They concluded that the current scientific evidence is not enough to suggest a conclusive recommendation for an optimal age for the timing of elective resection. We performed surgery in an earlier stage of infancy, namely 1-6 months old to reduce the risk of later complications like respiratory infections and pneumothorax (18). Formal lobectomy is the most commonly accepted surgical option for CPAMs in the current medical era (3) although in recent years some authors have suggested lung-sparing techniques such as segmentectomy by thoracoscopy for these lesions (19,20). However, these strategies comprise an increased risk for an incomplete surgical excision. The risk of bringing residual disease was reported as 15% after segmental resection (21). This approach should be rationale for salvaging from radical surgical resections such as pneumonectomy for multi-lobar or bilateral disease (22). In our study, we performed lobectomy for the major lesion and segmentectomy for the minor lesion in the left lobe to avoid pneumonectomy. In another patient with bilateral multilobar disease, we preferred multiple sessions of thoracoscopic wedge resections. We have not seen any recurrence or malignancy in the postoperative follow-up period. This surgical strategy which is based on the location of pulmonary involvement provides a safe and effective treatment option in bilateral and multilobar disease. These patients should be followed by regular radiological imaging studies. We preferred chest X-rays with 3-month-intervals in the first postoperative year. A computerized tomography should be obtained at the end of the first year of postoperative period.

Study Limitations

Due to the retrospective nature of this study, there may have some limitations. Larger number of the patients should be more useful to evaluate the results of the operative strategies.

Conclusion

In conclusion, we suggested lobectomy for single lobar pulmonary involvement, and lobectomy for major lesion lesion; and segmentectomy for the minor lesion in unilateral multi-lobar involvement; and multiple thoracoscopic wedge resections for bilateral multi-lobar pulmonary involvement.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: All of the parents gave their informed consent prior to their inclusion in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.D., Z.D., B.T., C.Ö., A.E., Concept: E.D., Design: E.D., Data Collection or Processing: B.T., Analysis or Interpretation: E.D., C.Ö., A.E., Literature Search: E.D., Z.D., Writing: E.D.

Conflict of Interest: None of the authors had conflict of interest.

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Original Article

Practical Aspects of the Use of Healthcare Failure Mode and Effects Analysis Tool in The Risk Management of Pediatric Emergency Department: The Scrutiny in Iran

Yasamin Molavi-Taleghani[1], Asma Abdollhayar[2], Mahmoud Nekoei-Moghadam[3], Hojjat Sheikhbardsiri[4]

[1]*Isfahan University of Medical Sciences, Health Management and Economics Research Center, Faculty of Management and Medical Informatics, Isfahan, Iran*
[2]*Kerman University of Medical Sciences Hospital Afzalipour, Master of Science in Nursing Orientation Ward Nicu, Kerman, Iran*
[3]*Kerman University of Medical Sciences Research Center for Health Services Management, Institute for Future Studies in Health, Kerman, Iran*
[4]*Kerman University of Medical Sciences, Department of Emergency Operation Center, Disasters and Emergencies Management Center, Kerman, Iran*

ABSTRACT

Aim: The Emergency Department is one of the most challenging wards of the hospital for studying patient safety and the prevention of treatment errors is the basic rule in the quality of health care. The present study was conducted to evaluate the selected risk processes of Pediatric Emergency of Qaem Educational Hospital in Mashhad by the Healthcare Failure Mode and Effects Analysis (HFMEA) methodology.

Materials and Methods: A mixed method was used to analyze failure modes and their effects with HFMEA. Five high-risk processes of the Pediatric Emergency were identified and analyzed. To classify failure modes, nursing errors in clinical management model; for classifying factors affecting error, the approved model by the United Kingdom National Health System; and for determining solutions for improvement, Theory of Inventive Problem Solving was used.

Results: In 5 selected processes, 28 steps, 80 sub-processes and 254 potential failure modes were identified with HFMEA. Thirty-seven (14.5%) failure modes as high-risk errors were detected and transferred to the decision tree. The most and the least failure modes were placed in the categories of care errors as 62.3%, and knowledge and skill as 8.1% respectively. Also, 23.6% of preventive measures were in the category of human resource management strategy.

Conclusion: Using the proactive method of HFMEA for identifying the possible failure of treatment procedures, determining the effective cause on each failure mode and proposing the improvement strategies, has high efficiency and effectiveness.

Keywords: Emergency, Healthcare Failure Mode and Effects Analysis, pediatric, risk management.

Introduction

Medical failure poses a real threat to both the health system and the patients' health. It is likely to happen in all diagnosis and treatment stages, which is often costly and reduces the quality of life of patients (1). Hence, maintaining patient safety is a major concern in the health care system (2). Furthermore, the Emergency Department is one of the most challenging departments of the hospital for for the study of patient safety because of its unique features (3). In emergency situations, time for critical thinking, which results in delays in decision making and consequently an increase

Address for Correspondence
Hojjat Sheikhbardsiri PhD, Kerman University of Medical Sciences, Department of Emergency Operation Center, Disasters and Emergencies Management Center, Kerman, Iran Phone: +98 913 279 31 99 E-mail: hojat.sheikhbardsiri@gmail.com ORCID ID: orcid.org/0000-0002-3264-6792
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in adverse events, is very short (3). Preventable errors are one of the main factors of patient death and disability. Based on the results of a study, nearly 40% of inpatients have become disabled, and 2.3% of these disabilities were related to preventable errors (4). Totally, 3% of all hospital errors are related to the emergency department (5). Furthermore, approximately one-third of the patients referring to hospitals are for the pediatric emergency department, and this department has been identified as a high-risk area in the health care system (6). Adverse events have resulted in an extra expenditure of about 37 billion US dollars in America, and one to two billion pounds in England (7). Prevention of medical errors is one of the basic principles in the quality of health care (7). In all quality improvement programs, an error prevention and risk management approach is one of the pivotal aspects of creating, establishing, and deploying management systems in organizations (8). One of the most promising risk prevention programs from the viewpoint of the National Center for Patient Safety (NCPS) and the US Accreditation Commission, is Healthcare Failure Mode and Effects Analysis (HFMEA) (9). In fact, HFMA is a systematic and predictive strategy which is designed specifically for healthcare organizations to identify and prevent errors before they happen (10). This method is used extensively in order to identify errors and improve patient safety standards. Results of studies indicate that from 2008 to 2009, and after the implementation of risk assessment programs by NCPS, the number of adverse medical events has reduced from 3643 to 2412 (11). The administration of patient safety plans in the Emergency Department has improved the quality of healthcare and patient satisfaction (12), and the Emergency Department is one of the most important departments of the hospital (13), as well as being the first department to provide healthcare for many patients (14). Therefore, the present study was conducted to evaluate the selected risk processes of pediatric emergency of a treatment-educational Qaem center in Mashhad by the HFMEA methodology.

Materials and Methods

Research Design and Setting

This study was approved by the ethical committee of Mashhad University of Medical Sciences prior to the collection of the data in January 2013 (approval number: 911089). Written informed consent was recruited from each participant. A mixed-method including qualitative action research and descriptive quantitative cross-sectional study was conducted in 2016. Qaem Hospital is ranked as one of the largest educational and therapeutic centers at regional and national levels, with a total of 870 active beds, 18 units and 7 emergency rooms, with Para clinical services and clinics. Children's Emergency Department of Qaem Hospital undertakes the following services: reception and outpatient treatment; performing, sending and following-up laboratory tests; serum attachment; physiotherapy; tension test; catheterization; electroencephalogram; performing, sending and following the response of the cerebrospinal fluid; vaccination, washing, wound dressing of the patient; patient's initial visit, nominal group technique, electromyography-nerve conduction velocity, magnetic resonance imaging (MRI), computed tomography scan; neonatal lactation; endoscopy; liver biopsy; primary visit; patient radiology, Sonography, suction, intubation, auditory test, optometry test, delivery of blood transfusion and blood products, phototherapy and determining the condition of the patient (transferring the patient to other departments for continued care or discharge). In this study five high-risk processes of pediatric emergency department were identified and analyzed in Qaem Treatment-Educational Center. It should be noted that the temporary admission rate in the Pediatric Emergency had an average of 396 people per month (200 temporary admissions in the morning shift, 110 admissions in the evening shift and 86 in the night shift) in 2015.

Data Collection

Data gathering was done through focus groups, interviews, observation, and brainstorming. The validity of this study was controlled by the consensus of team members at the end of each phase. The stages of this research were determined according to the five stages of the analysis of the states and effects of health care errors by the National Center for Patient Safety (9), and were carried out as follows, which, as the circumstances require, have differences with the proposed model;

Step 1: Choosing a Risky Process

Via the "voting method using rating" technique, ten members of the pediatric emergency department were asked to rank five of the 26 processes listed in the section, considering the problem effects on the patients' dissatisfaction, the likelihood of injuries by the problems and the need to fix the problems. Then, the data obtained from the voting was finalized according to the matrix or the Breda function and five priority processes were selected for risk management (15,16).

Step 2: Assembling the Team

Qaem Hospital's emergency staff includes a supervisor, 8 nurses, 3 staff members, one children's emergency department director, 5 pediatricians, a secretary, two crew members and 6 pediatric residents. In the staffing program, the staffing of the emergency medical staff is carried out three times morning, evening and night. In this process, 15 persons participated as the members of HFMEA team, including the responsible person of risk management (team leader), an expert in health services (team advisor), an assistant professor in the emergency department, head of the emergency department, a supervisor, two assistants

(residents), two nurses, the chief of the laboratory, a laboratory expert, a blood bank expert, MRI expert, and head of the MRI department.

Step 3: Graphically Describing the Processes

At this stage, the charts of the selected processes and their sub-processes were drawn through the observation and individual interviewing method, and the accuracy of the diagram of the flow of processes and sub-processes was modified and approved by the team members in a group discussion session, and was drawn in the form of a process flowchart with Visio software.

Step 4: Conducting Hazard Analysis that Took Place in Four Phases

First phase: Determination of potential failure modes

At this stage, the error states of each of the sub-processes of the selected sections were identified by the triangular method (17), and classified according to the classes of the "Nursing Error Management Association" model (18). Failure modes according to the nursing errors in clinical management model were categorized in 4 main groups of communication; care process, administrative, knowledge, and skilled based error (18).

Second Phase: Determination of the hazard score

The hazard Score was determined using the Error Scoring Matrix (the product of the two elements of the severity and probability of occurrence of the error) and was recorded in the HFMEA worksheet. The errors were grouped according to their hazard score into four intervention levels, i.e., emergency, urgency, programming, and monitoring (Table I) (19).

Third Phase: Designing decision making tree

The non-acceptable risks (risk score level more than 8) were transferred to the decision tree. Decisions for proceeding or stopping each of the failure modes was made based on three items; weakness points, existing control, and detectability.

Fourth Phase: In this phase, the failure mode causes of each failure mode, and where the decision is to "Proceed" were categorized into 9 root causes in the consultative cause-effect meetings, and in the format of an approved model by the UK National Health System (20).

Step 5: Actions and Measurement of Consequences which Were Performed in Two Phases

Table I. Error scoring matrix and classification of interventional levels

Intervention level	Severity& probability	Catastrophic (4)	Important (3)	Intermediate (2)	Minor (1)
Emergency	Usual (4)	16	12	8	4
Urgent	Sometimes (3)	12	9	6	3
Programming	Unusual (2)	8	6	4	2
Monitoring	Rare (1)	4	3	2	1

Phase 1: Definition of Error Control Strategies

In this phase, suggested coping strategies were proposed for the causes of errors in the decision tree in the form of acceptance, control, and elimination of errors. The second phase, redesigning the process: improving strategies for each cause of error with a score ≥8 in the team meetings through "theory of the problem solving by an inventive method" (21,22) were provided and classified with inspiring by the proposed model of "classification of preventive strategies in the incidence of medical errors" (7,23), and finally decisions were made about the practicability of the implementation of any approach with regard to the resources of the organization.

Statistical Analysis

Quantitative Analysis: For the quantitative analysis of the variables related to the failure mode analysis phase, descriptive statistics were calculated in Excel software, including frequency, percent, and mean. Also, for the quantitative analysis and determination of the probability of the failures, the sum of the team's scores was used with consideration of a coefficient for each team member. For the severity of the failures, the team members' consensus along with the consideration of weight for the severity of failures was used. In the final worksheet, we calculated and documented the sum of the failure mode severity scores according to team members' opinions. By considering weights for the failure mode severity dimensions we calculated the sum of the failure mode probability scores based on the involved personnel's opinions (also by considering the coefficient for each person).

Qualitative Analysis: Content analysis was done on the data collected from the individual interviews in order to put them in the organized forms. To do so, all the interviews with the team members were transcribed, and, for the sake of understanding the transcriptions, they were read, and repetitions were omitted and the significant issues were extracted. Therefore, a list of all of the team members' opinions was prepared. Analysis of the data from the brainstorming, cause and effect, and problem-solving sessions was done based on the general agreement of the team members. It should be noted that the time taken to carry out the study was 38 hours.

Results

By voting method using rating, 5 out of 20 identified processes in pediatric emergency, with Borda number of (37 score) for the process of MRI implementation (32 score) for the process of performing, sending and tracking the laboratory results (25 score) for the process of implementing the IP (18 score) for transferring CSF specimen and following up the results and (7 score) for the process of setup IV line, were chosen. According to the results, for 5 selected processes per 28 listed steps, 80 sub-processes and 254 failure modes were identified. According to table 2, the interventional levels showed that 1.2% of the error modes

Table II. Frequency distribution of failure modes in each area of the error scoring matrix and classification of failure modes based on the model of Management Association of nursing error for the selected emergency pediatric processes

High-risk processes of emergency pediatric	Activities	Number of sub-processes	Number of failure modes	Maximum hazard score	Minimum hazard score	Number of intervention levels categories				Frequency percentage of failure modes based on association model of "management of nursing error"			
						Emergency levels	Urgent levels	Programing levels	Monitoring levels	Care process error	Communication errors	Administrative errors	Knowledge and skill errors
Administration of lab tests, transferring and follow up	Order for lab test	6	19	9	2	0	3	14	2	17	7	0	1
	Sampling and transferring the sample	4	17	9	3	0	1	15	1	13	2	5	4
	Sample analysis	4	15	9	6	0	2	13	0	14	0	6	2
	Preparing test results	1	4	9	6	0	3	1	0	4	0	2	0
	Reporting the test result to the doctor	2	5	6	4	0	0	5	0	4	0	0	1
MRI	Order for MRI	2	7	9	4	0	2	5	0	5	1	0	1
	Informing the ward secretary about MRI order	3	11	9	2	0	1	8	2	4	3	1	2
	Reporting MRI order to MRI ward	3	8	6	4	0	0	8	0	3	5	2	0
	Transferring the patient to MRI ward	2	8	6	4	0	0	8	0	9	0	1	0
	MRI implementation	1	4	9	2	0	1	2	1	3	0	2	0
	Taking results and reporting that to the doctor	2	5	6	2	0	0	3	2	5	0	1	1
Transfusion	Doctor order for blood transfusion and checking doctor order	3	10	9	4	0	2	8	0	7	1	5	1
	Sampling	4	13	6	3	0	1	10	2	12	3	2	1
	Administration of required tests before transfusion	5	14	12	3	2	3	9	0	8	3	4	0
	Requesting blood from blood bank by pediatrics emergency ward	3	10	12	4	1	2	7	0	7	1	1	0
	Reception of blood from blood bank by pediatrics emergency ward	2	4	6	4	0	0	4	0	3	0	1	0
	Implementing required actions before transfusion	3	13	8	4	0	2	11	0	9	3	1	0
	Starting blood transfusion	2	7	8	4	0	2	5	0	5	3	0	0
	Recording transfusion in the patient file	2	6	9	4	0	1	5	0	0	4	1	0
Implementing LP, transferring CSF specimen and following up the results	Doctor order for LP	2	8	9	3	0	2	4	2	8	2	2	0
	Preparing equipment and administrating LP	4	14	9	2	0	3	5	6	15	3	2	2
	Preparing and transferring CSF specimen to the lab	3	8	6	4	0	0	8	0	3	0	6	0
	Preparing results by the lab	3	9	9	4	0	2	7	0	8	0	3	1
	Transferring result to the doctor, interpretation of the results and starting action based on the result	2	3	6	4	0	0	3	0	3	0	1	1

Table II. Continue													
IV line setup	Checking for doctor order	2	4	4	4	0	0	4	0	3	1	1	0
	Preparing IV set	4	9	9	4	0	1	8	0	10	2	1	2
	Setting up IV line	4	12	6	2	0	0	9	3	12	2	1	5
	Patient observation and recording IV line setup	2	7	4	2	0	0	5	2	8	2	0	0
Total		80	254	214	98	3	34	194	23	202	45	51	26

Hint: It may put failure modes in different categories based on management association of nursing error, CSF: Cerebrospinal fluid, LP: Lumbar puncture, MRI: Magnetic resonance imaging, IV: Intravenous

Table III. Classification of the basic causes of failure modes with error score ≥8 based on Eindhoven model

Error cause	Setup IV line	Laboratory management	Delivery, transfusion of blood and blood products	MRI implementation	Implementing LP, transferring CSF specimen and following up the results	Total root causes based on effective factors
Factors related to patient and patient caregiver	1	1	1	1	6	10
Factors related to personnel	0	3	6	2	2	13
Task factors	0	2	6	0	0	8
Communication factors	1	4	3	3	2	13
Equipment factors	0	3	3	0	1	7
Environmental factors	0	6	8	1	2	17
Organization factors	0	2	3	2	1	8
Educational factors	1	6	7	1	5	20
Team factors	1	2	4	2	1	10
Total root causes based on the process	4	29	41	12	20	106

CSF: Cerebrospinal fluid, LP: Lumbar puncture, MRI: Magnetic resonance imaging IV: Intravenous

were related to the emergency levels intervention, 13.3% to urgent, 76.3% to programmed, and 9.1% were related to the monitoring area. Also, the number of identified failure modes, the number of intervention levels and the classification of the failure modes for the selected processes based on the proposed model were shown by the association of "management of nursing error". According to Table II, (62.3%) of the failure modes related to care process error; (13.8%) to communication errors; (15.7%) to administrative errors; and (8.1%) to knowledge and skill errors. In the next step, from the 254 detected failure modes, 37 (14.5%) were recognized as high-risk and unacceptable (hazard score of 8 and higher) and were transferred to the decision tree (Table III). In Table III, classification of the causes of high-risk and non-acceptable risk (hazard score ≥8) is shown based on an approved model by the UK National Health System. According to table 3, among the 106 effective causes detected in the high-risk failure modes of the decision tree, 9.4% related to team factors; 7.5% to organizational factors; 12.2% to communication factors; 7.5% to task factors; 12.2% to personnel factors; 16.1% to environment factors; 9.4% to patient factors; 18.8% to education factors, and 6.6% to facilities and technologies. Table IV, Phase I, Definition of Error Control Strategies: In this phase, suggested coping strategies were proposed for the causes of errors in the decision tree in the form of acceptance, control, and elimination of errors. Strategies suggested opposing the contributing factors to each failure mode were presented in the forms of acceptance (25%), control (58.3%), and elimination (16.6%). In Table V, the strategic classification and preventive approaches proposed by the problem-solving theory are shown based on the proposed model. According to Table V, among the 106 strategies detected in the high-risk failure modes of the decision tree, 23.6% related to human resource management; 2.9% to the installation of electronic prescribing system; 5.9% related to making people accountable for patient's safety; 5.9% related to medical equipment management and process standardization; 4.1% to the improvement of the patient identification process; 2.6% related to making clear and transparent policies and procedures; 3.2% to making sure of the availability of a suitable technology for quality improvement; 7.6% to the continuous training and briefing of care providers at the beginning of employment; 11.2% related to the participation

Table IV. The worksheet of failure modes techniques and Healthcare Failure Mode and Effects Analysis for some high-risk failure modes of the selected pediatric emergency processes

Hazard analysis									Action and outcome measures	
Failure mode	Potential causes	Scoring			Decision tree analysis			Proceed	Action type	Actions or rationale for stopping
		Severity	Occurrence	Hazard score	Weakness point	Existing control measures	Detestability			
Slip in checking the blood request form by the blood bank while delivering the blood bag	→	3	4	12	→	No	No	Yes		
	A) temporal high work load of blood bank	3	2	6	no	-	-	No	A	1) Stress management and tasks distribution
	B) Lack of awarness of importance of the issue and necessary evaluation by the blood bank	3	3	9	→	No	No	Yes	C	1) Developing the staff performance evaluation scales, based on the mistake that occurred 2) Annual evaluation of personnel of appropriate blood transfusion process 3) Training physicians about the "right patients, right time and right blood" guideline 4) Training on compliance with accreditation requirements 5) Root cause analysis about catastrophic events and giving feed back to the blood bank
	C) Lack of readability of request form	2	3	6	→	No	Yes	No	E	1) Training on and implementation of principles of registering reports and request form 2) Rejecting the unreadable form by the blood bank
Ask the patient for MRI request	→	3	3	9	→	No	No	Yes		
	A) MRI cancellation and not implementing it	3	3	9	→	No	No	Yes	C	Healthcare team collaboration-review of inter ward transfer policy-constant observation of head of the ward on ward and during patient transfer
	B) Not knowing about the results	3	1	3	→	Yes	-	No	E	Using PACS system-informing the doctors about the results
Delay in initiation of testing the samples in laboratory	→	3	4	12	→	No	No	Yes		
	1) Crowded laboratory	3	4	12	→	No	Yes	No	A	1) Reducing the workload and creating shift table and preventing successive shifts 2) Providing extra work force 3) Fitting the workload with number of human forces 4) Coordinating the treatment team and establishing stress management
	2) Lack of awareness of importance of the issue	3	3	9	→	No	No	Yes	C	1) Holding briefing sessions at the beginning 2) Appoint a leader or head for the team 3) Sharing the information with treatment team
	3) Lack of supervision of technical manager on procedures	3	3	9	→	No	No	Yes	C	1) Periodic monitoring and evaluation of laboratory ward 2) Checking the competence of team leader or the responsible person 3) Monitoring temporal sequence of process

Table IV. Continue

Lack of patient cooperation during sampling	→	3	3	9	→	No	No	Yes		
	1) Patients fear specially children from medical procedures	3	4	12	→	No	No	Yes	A	1) Increasing patient knowledge by effective communication and patient participation 2) Assessing patient communication ability with healthcare provider 3) Providing patient with information
	2) Lack of right communicat-ion between patient and healthcare providers	3	3	9	→	No	No	Yes	C	1) Providing patient with information and consequences of procedures 2) Administrating topical anesthesia before LP
Desterilizing of IV set by patient caregiver	→	3	3	9	→	No	No	Yes		
	1) Lack of patient caregiver knowledge	3	2	6	→	No	No	Yes	C	1) Informing patient caregiver about the type of the procedure 2) Informing patient about consequences of each procedure 3) Advising patient not to interfere in the care process
	2) Lack of medical team observation on ward	3	2	6		No	No	Yes	C	1) Holding teamwork training workshops for all team members 2) Devising Plans for patient safety 3) Cooperation of healthcare team

Hint E: Elimination, C: Control; A: Accept MRI: Magnetic resonance imaging, PACS: Picture archiving communication systems, IV: Intravenous, LP: Lumbar puncture

Table V. Classification of strategies and preventive measures for causes of high risk error modes (risk score ≥8)

Ward Strategy classification	Improvement strategy by means of the TRIZ method	Intravenous	Blood and blood products transfusion	MRI	Laboratory management	LP	Total
Human resources management	Determination of a supervisor for treatment team, evaluation of the competency of team leader, conducting periodical assessment and offering feedback to the personnel, giving treatment team the necessary information, defining the responsibilities and announcing them, reducing the work load and correcting the lack of work forces, continuous supervision and controlling the performance procedures and adjusting the workload with staff	1	30	7	32	10	80
Installation of electronic prescribing system	Implementation procedure on drug combination	0	0	0	1	0	1
Making people accountable for patient's safety	Culturally appropriate environment for patient safety and deployment of an incident reporting system, encouraging the staff to ask question in case of obscurity and resolving the issue of lack of man power, detachment and pursuing the test results in form of root analysis of the events and reporting the critical results	0	11	1	5	3	20
Medical equipment management and process standardization	Regular calibration of medical equipment, emergency service of medical equipment and devices, checklists for maintenance of the tools and facility management, purchasing of protective equipment, creating a qualitative committee and monthly views of the equipment of Radiology unit. Purchasing safety equipment for safe transfer	0	10	3	6	1	20
Improvement of patient identification process	Applying key identifiers in patient identification, improvement of the patient's recognition processes and revising the guidelines for the correct recognition of the patients	0	8	0	6	0	14
Making clear and transparent policies and procedures	The re-engineering of the process, preparing and organizing the executive guidelines and protocols such as right drug administration, blood transfusion, IV therapy, care of connections and catheters, inter and intra ward transfer, preparing new forms with special parts, facilitating the processes and removing the unnecessary steps, designing a special check-list for evaluation of the patient's transition between emergency and radiology units, revision policies, simplifying the process and eliminating unnecessary steps and audits process	0	5	1	2	1	9

Table V. Continue							
Making sure about availability of suitable technology for quality improvement	fundamental improving of the software for entering the physician's commands for tests-providing PACS system in order to ease the access of experts to MRI	0	3		8	0	11
Continuous training and briefing care providers at the beginning of employment	The re-training courses and preparing proper training content according to the needs of the personnel, the scientific training for prescription writing and continuous medical training for the physicians, training of recommendation and instructions, continuing the re-training programs for physicians, training of recommendation and instructions	1	14	3	0	8	26
Participating patients in treatment process	His/her accompanying person and teaching all the regulations of the sector and offering the sufficient data and patient's training, patient's contribution by making effective relationship with them, development of educational patients	3	2	2	12	19	38
Implementing and monitoring suitable changes in clinical processes based on analysis of reliable data	Continuous supervision, defining the periodical performance assessment criteria and providing feedback to the personnel, introducing a reference laboratory and performing some of the important tests randomly in various periods as binary tests by the hospital laboratory and the reference lab, monitoring on following up standards. Taking conscious agreement and explaining probable side effects and risks of lumbar puncture procedure to the patient or to the patient caregiver	0	22	1	2	2	27
Promotion of communication amongst treatment team members	Not using abbreviations, obeying the oral commands only in urgent cases	0	2	2	22	1	27
Team work	Coordination of treatment team and improving the team relations	1	30	5	22	7	65
Total		6	137	25	118	52	338

IV: Intravenous, MRI: Magnetic resonance imaging, PACS: Picture archiving communication systems, TRIZ: Theory of inventive problem solving

of the patients in the treatment process; 7.9% related to implementing and monitoring suitable changes in the clinical processes based on the analysis of reliable data; 7.9% to the promotion of communication amongst the treatment team members, and 19.2% related to team work.

Discussion

In this study, according to the five steps for diagnosing the states and effects of health care errors, proposed by the National Center for Safety of The Patient, we identified the possible errors of the selected childhood emergency procedures, the causes of each error situation and the identification of remedial measures. However, with the requirements of the study, changes were made to the proposed model to eliminate model constraints in the implementation. The major changes are: 1) Selecting high-risk processes by voting, using ranking approach, 2) Classifying errors in the framework of nursing error management model, 3) Designing more comprehensive methods to determine the error rate level, 4) Failure factors classification based on the approved model by the UK National Health System; and 5) Failure classification within the framework of medical failure preventive strategies classification model. To prioritize and select the high-risk processes, voting method using rating was used with the study of Taleghani et al. (24) that is consistent in selecting the high-risk process while Anderson et al. (17) used the risk-assessment matrix and the average error score for the selection and periodization of high-risk process in the surgery department. In the present study, the multidisciplinary team was used to identify and assess risk in the pediatric emergency department. Study results of Dominici indicate that in order to evaluate the results of the application effect of HFMEA in the quality of patient care, creating multidisciplinary teams to identify and classify possible risks is important (25). Since the first step in reducing health care errors is to identify the failure modes, a comprehensive model must be used to categorize all failure modes, and help to identify and compare them (26,27). Therefore, we used Nursing Error Management model to group the failure modes of the selected processes in pediatric emergency. In the present study, the most common error related to the care process error in the classes (errors in clinical judgment, errors in caring procedures and continuity of care errors) had 62.3% prevalence, and was followed by administrative errors in the classes (error in monitoring and planning of the organization and lack of proper management of the organization) with 15.7%. According to the results of the study by Ebrahimipour et al. (7), the most failure modes were in the categories of care errors (63.3%), administrative errors (15.8%), communication errors (10.9%), and knowledge and skill errors (9.7%), which is consistent with the results of the present study. In most of the studies with the HFMEA method, the variable of ability to detect failure mode has been eliminated, the reason being that the concept of detection risk is hidden in the indicator of the degree of

occurrence and the low possibility of discovering the many risks of the health sector (20). If the error report systems in the healthcare sector is applied comprehensively and as a general system in the country, the problem will be resolved (28). In the present study, the incidence and error possibility was determined individually and independently. Independent scoring of team members has the advantage of wearing off the halo effect (cognitive bias caused by an observer's overall impression of a person or situation), which exists in group discussions (17). In this study, all failure modes were classified into one of the following intervention levels based on their hazard score: emergency, urgency, programming, and monitoring. The advantage of this method is that because of the lack of resources of organization, corrective actions and focus on reducing the risk of errors is due to the levels of intervention (19). According to the results of Najafi et al. (29), 52 errors in the process of using Entonox for labor pain as 5.7%, 21.1%, 26.9%, and 46.1% were placed in the intervention area of monitoring, emergency, urgency and programming respectively, a finding consistent with our findings here (29). One of the advantages of HFMEA is prioritizing causes which affect all aspects of errors (30). In this study, by using cause and effect analysis, root causes of errors were classified into nine levels of the confirmed model of England National Organization. The most frequent causes of errors were training factors (18.8%) and environmental factors (16.1%). In another study using the HFMEA approach, lack of knowledge and skill are reported to be effective causes of high-risk errors in transferring the patient from the neonatal intensive care unit to the acute care unit (31). In the study of Dehnavieh et al. (27) the most frequent cause of errors in blood transfusion procedure was training factors (27.2%), which is compatible with the results of the present study. In a study by Steelman et al. (32), 34.9% of the causes of high-risk errors identified by HFMEA in the management of retina disorders were reported to be excessive work pressure, doing all the procedures at the same time, and failure in environment design, also compatible with the results of this study. Kositchaiwatet al. (33) reported that the most important causes of medication errors of outpatients were environmental factors (24%), similar to the results of the present study. Considering the limited resources in any health care organization, the cost of the most effective ones should be chosen to implement strategies and address the causes of the error (27). Therefore, in this study, to determine the proposed strategies, "theory of the problem solving by an inventive method" was used. According to the results of this study, the most preventive measures in selected childhood emergency were grouped in the category of human resource management, team work strategies, and team work. Human resource management strategies are the first ways that organizations can apply to shape individuals' skills, attitudes and behaviors, and thus achieve optimal performance for organizational goals (34). Through this strategy, senior health department executives identify and develop solutions for human resource issues (35). According to Taleghani et al. (24) and Ebrahimipour et al. (7), using the strategy of human resources management is the most important strategy to improve patient safety and reduce clinical errors. Team work strategy is an approach to develop communication among the health unit personnel who work separately in order to improve healthcare (36). Efficient team work depends on effective communication between team members and sufficient organization source. Compatibility with standard equipment and behavior is an effective strategy to improve team work morale (37). In a retrospective study, results showed that by implementing team work improvement strategies, 18% of the death rate in 74 training hospitals had decreased (38). According to O'leary et al. (39) and the National Society of Accreditation Commission, quality and patient safety depend on team work (39,40). Since the most prevalent errors in the researches of this field pertains to implementation and care errors, the following solutions are placed as executive orders on the agenda of the Ghaem Emergency Department: "Audit and re-engineering key emergency processes", "Providing and developing policies, and procedures such as checking doctor's orders, taking care of fittings and catheters, and identifying the patient", "Written job descriptions for personnel and its notification", "Compilation of personnel performance assessment criteria and periodic evaluation and feedback to personnel", "Designing educational content tailored to the needs of employees", "Reducing labor load and eliminating shortages of human resources", "Observing effective communication with the patient and in the form of patient education programs", "Continuation of retraining programs for the treatment staff", "Training recommendations and guidelines and monitoring compliance with standards", "Determining the critical scale for experiments", "Designing a special checklist for assessing the transfer of the patient from the ward to the MRI section", "Formation of the quality committee and monthly inspections of the equipment of the support department", "Promotion of collaborating", "Equipment Management", "Providing Pix system for easy access to the MRI photos by experts", "Getting informed consent and describing the possible complications and possible risks of carrying out the process of cerebrospinal fluid to the patient or the associate", "Using a patient identification bracelet", "The establishment of the blood transfer system", "Setting regular schedules for sending samples and receiving answers "and "monitoring the correct fitting". Finally, the utility of HFMEA has been proven in the redesigning of the health sector processes. However, successful implementation of this approach is associated with a strong and effective leadership and a continuing commitment to prevention (41). Latino and flood (42), had similar views on the role of leadership and organizational management in the successful implementation of risk management practices. It should be noted that the implementation of strategies and proposed actions have a strong relationship with team participation of the individuals, and financial and administrative support of the organization's

leader (20). So, the successful implementation of prospective risk assessment programs are related to the strong and effective leadership and continuous commitment of the director (42).

Study Limitation

One of the limitations of this study, and of all studies that use the HFMEA approach, is that showing a decrease in the probability of occurrence of adverse events is difficult after conducting interventions; thus, one cannot prove the improvement of the patients' safety or do cost-benefit analysis by using HFMEA programs (21). Also, the high risk errors in each organization are determined based on the atmosphere and environment of that organization, and the results cannot be compared with other organizations and even other departments of the hospital because the frequency and severity of errors differ in the same departments of different hospitals.

Conclusion

Using the proactive method of HFMEA for identifying the possible failure of treatment procedures, determining the effective cause on each failure mode and proposing the improvement strategies, has a high efficiency and effectiveness. So HFMEA should be implemented continually as a risk assessment model in healthcare organizations. Their application can reduce the occurrence of failures and their outcomes to the minimum possible level and provide a basis for quality improvement and risk reduction. Also, the application of systematic and regular proactive risk management techniques, along with the commitment of managers and the organization policies renewal can ensure the effectiveness of these activities.

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Ethics

Ethics Committee Approval: This study was approved by the ethical committee of Mashhad University of Medical Sciences prior to the collection of the data in January 2013 (approval number: 911089).

Informed Consent: Written informed consent was recruited from each participant.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.M.T., Concept: Y.M.T., Design: H.S., Data Collection or Processing: A.A., Analysis or Interpretation: M.N.M., Literatur Search: Y.M.T., H.S., Writing: H.S.

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Original Article

Evaluation of Children with Congenital Heart Disease Hospitalized with the Diagnosis of Lower Respiratory Tract Infection

Yasemin Özdemir Şahan[1], Erhan Kılıçoğlu[2], Zülal Ülger Tutar[1]

[1]*Ege University Faculty of Medicine, Department of Pediatric Cardiology, İzmir, Turkey*
[2]*Ege University Faculty of Medicine, Department of Pediatrics, İzmir, Turkey*

ABSTRACT

Aim: Lower respiratory tract infections are an important reason for mortality and morbidity in children with congenital heart disease. This study aimed to evaluate 50 children who had congenital heart disease and were hospitalized with lower respiratory tract infection in the Ege University Faculty of Medicine Pediatrics Hospital.

Materials and Methods: Fifty pediatric patients were taken into the study. Their clinical symptoms, acute phase reactants, chest X-rays, bacterial culture of transtracheal aspirate, respiratory virus panel (with multiplex polimerase chain reaction) from nasopharyngeal swab were examined. The groups were evaluated in terms of age, gender, enviromental smoke exposure, living with school-aged siblings, Respiratory Syncytial virus (RSV) prophylaxis, hospitalization time, causative pathogen, additional risk factors.

Results: Of the 50 cases, 12 (24%) were cyanotic, 38 (76%) were acyanotic. There were 26 boys and 24 girls. The most common diagnosis in the acyanotic group was hemodynamically significant VSD (isolated or with other diagnoses) with 20 cases. The average age of the cyanotic group was 23.88±28.81, and the acyanotic group was 12.25±15.45 months old. Hospitalizations most frequently occured in winter. The most frequent viral agent was RSV, which was not seen in the cyanotic group. All of the RSV infected patients were under 12 months old. In 16.7% of cyanotic and 52.6% of acyanotic patients there were extra risk factors such as immune deficiency, Down syndrome, prematurity, Di George syndrome, cerebral palsy, postoperative early period. Three cases lost their lives due to severe respiratory failure. There was no statistically significant difference between the two groups when compared for demografic variables, risk factors, causative pathogens, hospitalization times.

Conclusion: Lower respiratory tract infections and especifically RSV pneumonia are important causes of mortality and morbidity in patients diagnosed with congenital heart disease. To prevent risk factors, more studies must be done.

Keywords: Respiratory, infections, congenital, heart, disease

Introduction

The incidence of congenital heart disease (CHD) in the general population is about 1% and varies from 4/1000 to 50/1000 live births (1). Children with CHD have many complications concerning all of the organ systems, the respiratory system being the most important. Lower respiratory tract infection (LRTI) is a serious mortality and morbidity reason for children with CHD. Hemodynamically significant-CHD (HS-CHD) with pulmonary congestion poses a higher risk for LRTI and hospitalizations. Respiratory Syncytial virus (RSV) pneumonia is commonly seen in the first two years of life (2). Socio-economic and environmental risk factors such as prematurity, male sex, living with school-aged siblings, exposure to environmental smoking may increase susceptibility to RSV disease and frequent hospitalizations (3,4). In this study, 50 children with CHD, who were hospitalized with the diagnosis of LRTI, were analyzed in the Ege University Faculty of Medicine Pediatrics Hospital.

Address for Correspondence
Yasemin Özdemir Şahan MD, Ege University Faculty of Medicine, Department of Pediatric Cardiology, İzmir, Turkey
Phone: +90 506 291 58 24 E-mail: dr.yaseminozdemir@gmail.com ORCID ID: orcid.org/0000-0003-4219-9532
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Materials and Methods

Fifty pediatric CHD patients, aged from 1 to 108 months, hospitalized with LRTI between December 2013 and 2015 were included in our study. Ege University Faculty of Medicine Ethics Commitee approved the study (approval number: 14-11/11). After being informed of the purpose and content of the study by the doctor and having read the information for patients, all the parents gave written informed consent. Exclusion criteria was refusal of parental consent to participate in the study. The eligible patients were evaluated prospectively. For these patients who were previously diagnosed or had recently been diagnosed with CHD, acute phase reactants, postero-anterior chest X-rays, bacterial culture of transtracheal aspirate, respiratory virus panel (with multiplex polimerase chain reaction) from nasopharyngeal swab were examined. Demographic and clinical data were collected from the parents. The patients were classified into two groups as cyanotic and acyanotic. The groups were examined in terms of age, gender, demographic features, additional risk factors, exposure to smoke, living with school-aged siblings, having received palivizumab prophylaxis dose, hospitalization time, causative pathogen and complications.

Statistical Analysis

All continuous variables were analyzed using standard descriptive statistics with mean ± standard deviation values. As qualitative variables, median, minimum and maximum values were expressed. For non-normal distribution of independent measures, Mann Whitney U test was applied to the number of categories falling into two and Kruskal Wallis H test was applied to the number of categories falling into three or more. The data sets in categorical structures were analysed with chi-square (Yates&Fisher). Statistical significance was defined as $p<0.05$. All data analysis is was done with SPSS v21.0 (IBM Corporation, Armonk, New York, USA) software.

Results

Of the 50 cases, 12 (24%) were diagnosed with cyanotic and 38 (76%) with acyanotic CHD. Boy/girl ratio was 26/24. In the acyanotic group, 6 cases (12% of 50 patients) were diagnosed with venticular septal defect (VSD) and atrial septal defect (ASD); 6 cases (12%) with only VSD, 4 cases (8%) with only ASD; 4 cases (8%) with patent ductus arteriosus (PDA), 4 cases (8%) with endocardial cushion defect, 1 case (2%) with PDA+ASD, 1 case (2%) with aortic coarctation (AC), 2 cases (4%) with double outlet right ventricle (DORV) repair, 1 case (2%) with repair of tricuspit atresia (TA) with Fontan procedure, and 1 case (2%) with repair of d-transposition of great arteries with Jatenne procedure. All the other cases had mixed type of diagnostics including VSD. In the cyanotic group, 4 cases (8%) were diagnosed with Tetralogy of Fallot (TOF), 4 cases (8%) with DORV, 2 cases (4%) with truncus arteriosus, 1 case (2%) with pulmonary atresia, 1 case (2%) with TA. The average age of the patients diagnosed with cyanotic CHD was 23.88±28.81 months, and that of the acyanotic CHD patients was 12.25±15.45 months. Six (50%) of the cyanotic and 28 (73.7%) of the acyanotic patients were infants. Seven (58.3%) of the cyanotic and 27 (71.1%) of the acyanotic patients were living with 2 or more school-aged siblings. Five (41.7%) of the cyanotic and 12 (31.6%) of the acyanotic patients had been exposed to environmental smoke (Table I). There was no statistically significant difference between the groups when compared for demografic variables, passive smoking, LRTI with viral or bacterial agent, and hospitalization time. Twenty-six of 38 acyanotic patients (68.4%) had HS-CHD before 2 years of age, and 18 of 26 (69.2%) patients received palivizumab prophylaxis dose because the other 8 patients' hospitalization was a long time away from the RSV season. In the acyanotic group, the average dose of palivizumab received was 2.30±2.04. Of the 12 cyanotic patients (66.6%), 8 received palivizumab prophylaxis at an avarage dose of 2.44±1.68. Four of them could not receive the prophylaxis because of same reason as the 8 patients in the acyanotic group. Two of the cyanotic (16.7%) and 20 of the acyanotic patients (52.6%) had extra risk factors such as immune deficiency, Down syndrome, prematurity, Di George syndrome, cerebral palsy, postoperative early

Table I. Demografic variables between two groups and p values

	Cyanotic n=12 (%)	Acyanotic n=38 (%)	p value
Sex			
Female	6 (50)	17 (44.7)	0.958
Male	6 (50)	21 (55.3)	
Age			
<12 months	6 (50)	28 (73.7)	0.163
≥12 months	6 (50)	10 (26.3)	
School-aged siblings			
1	5(41.7)	11 (28.9)	0.438
2 or more	7(58.3)	27 (71.1)	
Exposure to smoke			
Yes	5 (41.7)	12 (31.6)	0.728
No	7 (58.3)	26 (68.4)	
Causative viral agent			
Yes	2 (16.7)	7 (18.4)	1.000
No	10 (83.3)	31 (81.6)	
Causative bacterial agent			
Yes	1 (8.3)	4 (10.5)	1.000
No	11 (91.7)	34 (89.5)	
PICU admission			
Yes	1 (8.3)	13 (34.2)	0.076
No	11 (91.7)	25 (65.8)	

PICU: Pediatric intensive care unit

period. Hospitalizations most frequently occured in winter (17 cases, 34%), and secondly in spring (14 cases, 28%). Viral agents were detected on the nasopharyngeal swab of 2 cyanotic patients (16.7%) and 7 acyanotic patients (18.4%). RSV was the most frequent viral agent which was isolated in totally 5 patients diagnosed with PDA, VSD+ASD, operated DORV and isolated VSD, (2 patients had viral co-infections including RSV determined below). Bocavirus was found in 2 cases diagnosed with VSD and DORV, and influenza B was found in 1 case diagnosed with VSD. In 3 other cases, viral co-infections found were influenza A and Rinovirus in 1 case diagnosed with TOF; RSV and Parainfluenza virus in 1 case diagnosed with PDA and RSV; Parainfluenza, Rhinovirus and Human Metapneumonia virus in 1 other case diagnosed with VSD. RSV was not seen in the cyanotic group (p=0.305). Three of 5 RSV infected patients (60%) were hospitalized in winter. Therefore, these patients received incomplete RSV prophylaxis. Similarly, 5 of the total 9 viral agent (+) patients (55.6%) were hospitalized in winter (Table II). All of the RSV infected patients were under 12 months of age. Two of them had extracardiac risk factor (Down syndrome and prematurity with bronchopulmonary dysplasia). One (8.3%) of the cyanotic patients who was a two-year-old boy with tracheostomy cannula and home ventilator had bacterial LRTI. The agent was Haemophilus influenzae. Four (10.5%) of the acyanotic patients had also had bacterial LRTI. These were respectively 2,7,2 and 54 months old, and the agents were Stenotrophomonas maltophilia, Klebsiella pneumoniae, Pseudomonas aeruginosa. The second and fourth patients had neurological sequelae and cerebral palsy. Unfortunately, the first patient have been lost died in the pediatric intensive care unit (PICU) after surgery of severe AC with respiratory system complications. One of the cyanotic patients who was aged 3 months, diagnosed with DORV and admitted to the PICU died due to respiratory failure. He had had no extracardiac problems and no viral or bacterial agents were detected. Thirteen of 38 (34.2%) acyanotic patients needed PICU admission (p=0.076), 2 of them died because of acute Respiratory Distress syndrome aged 2 months and 2 years, and they had had no extracardiac problems either.

Table II. Viral agent frequency related season

Viral agent		Frequency (n)	%
(+)	Winter	5	55.6
	Summer	1	11.1
	Spring	3	33.3
	Autumn	0	0
	Total	9	100.0
(-)	Winter	12	29.3
	Summer	7	17.1
	Spring	11	26.8
	Autumn	11	26.8
	Total	41	100.0

The first patient had a bacterial agent, Stenotrophomonas maltophilia. Viral and bacterial agents were not found in the second patient. There was no statistically significant difference between the two groups (Table I). When compared for hospitalization times, there was no significant difference between the type of CHD, season, age and viral agent (Table III).

Discussion

LRTI are defined in the International Classification of Diseases as infections that affect airways below the epiglottis (5). Some children have predisposing risk factors such as prematurity, CHD, chronic lung disease, immune disorders, being below 5 years of age, enviromental smoke exposure, oropharyngeal incoordination with Aspiration syndrome (6-9). Also children with HS-CHD with congestive heart failure are more at risk for LRTI causing mortality and morbidity (10-12). Incidence of CHD differs for populations and the most common type of CHD is VSD (1). Some kind of CHD which leads to increased pulmonary flow (e.g. VSD, PDA) or CHD with desaturation (e.g. TOF, DORV, truncus arteriosus) carries a higher risk of recurrent respiratory tract infections and increased frequency of hospitalizations (2). According

Table III. Hospitalization time between the groups and p values

	Hospitalization time (day) Mean ± standart deviation Median (minimum-maximum)	p value
CHD		
Cyanotic	12.68±11.909 9.0 (4-53)	0.239
Acyanotic	13.53±7.357 12.0 (3-30)	
Season		
Winter	12.35±8.046 10.0 (3-30)	
Summer	15.5±8.602 15.5 (5-26)	0.578
Spring	10.78±4.838 10.0 (4-21)	
Autumn	16.18±13.526 15.0 (4-53)	
Age		
<12 months	14.69±10.048 13.0 (3-53)	0.114
≥12 months	10.47±5.535 9.0 (4-23)	
Respiratory viral panel		
Agent +	9.44±5.228 9.0 (3-20)	0.119
Agent -	14.09±9,412 12.0 (4-53)	

CHD: Congenital heart disease

to a review of 38 studies, especially HS-CHD patients with pulmonary congestion before the age of 2 are more likely to be hospitalized with severe RSV infections (13). In our study, similar to the literature, acyanotic CHD, especially VSD was the most frequent patient group that needed hospitalization for LRTI. We saw that children with pulmonary congestion were more at risk for PICU admission. Acute respiratory tract infections of childhood are usually seen before the age of 2. The American Academy of Pediatrics has included children with HS cyanotic CHD and acyanotic CHD, bronchopulmonary dysplasia, and prematurity in the high risk group for RSV infection, extended the age limit to 2 years, and recommended RSV prophylaxis (14). According to one study from China with 2721 hospitalized children those who were under 6 months old and who had CHD carried a higher risk of severe RSV disease (15). In our study 68% of the patients were younger than 12 months, 84% were younger than 24 months of age, similar to the literature (16-17). Medrano et al. (3) carried out CIVIC Epidemiologic Study with children who had HS-CHD, and found significant associated risk factors such as previous respiratory disease, incomplete immunoprophylaxis against RSV, Di George syndrome, Down syndrome, cardiopulmonary bypass, and siblings aged less than 11 years old. In the study, the most commonly identified infectious agent was RSV, like in our study. Also one study from Turkey by Ozyurt et al. (18) revealed that children having CHD without RSV prophylaxis are more at risk for complicated LRTI, LRTI-related hospitalization, and intensive care unit admission. They also stated that patients with prophylaxis in the presence of siblings under the age of 12 and and with congestive heart failure suffer from LRTI-related hospitalizations (18). Down syndrome with or without CHD is a risk factor leading to mortality or hospitalization (4). Similarly, in our study some patients had extracardiac risk factors and 4 of these patients were in early postoperative period after cardiopulmonary bypass (7 patients with Down syndrome and 1 patient with Di George syndrome, 7 patients with prematurity, 1 patient with congenital adrenal hyperplasia, 16/50). Additionally, in our study all of the patients had at least 1, and 68% of the patients had 2 or more school-aged siblings. As we think that school-aged children act as a carrier, living with school-aged siblings increases the risk of LRTI and also the morbidity of LRTIs. Passive smoking or enviromental smoke exposure is also a risk factor causing recurrent LRTI (19,20). But in contrast to the literature, in our study more than half of the patients had not been exposed to cigarette smoke. Hospitalization most commonly was seen in winter (34% of all hospitalizations) but there was no significant difference regarding the hospitalization time of the patients in our study (Table II).

Study Limitations

The most important limitation was the number of patients in the study.

Conclusion

In this study we report children with CHD, hospitalized in a single center having been diagnosed with LRTI; the demografic variables, risk factors, infectious agents causing mortality and morbidity in the light of the literature. To prevent these risk factors more studies must be done.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Faculty of Medicine Ethics Commitee (approval number: 14-11/11).

Informed Consent: After being informed of the purpose and content of the study by the doctor and having read the information for patients, all the parents gave written informed consent.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K., Y.Ö.Ş., Z.Ü.T., Concept: Z.Ü.T., Design: Y.Ö.Ş., Z.Ü.T., Data Collection or Processing: E.K., Y.Ö.Ş., Analysis or Interpretation: E.K., Literature Search: Y.Ö.Ş., Writing: Y.Ö.Ş., Z.Ü.T.

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Original Article

Vitamin D Deficiency in Premature Infants and Its Effects on Neonatal Prognosis

Demet Terek, Gizem Özcan, Fırat Ergin, Özge Altun Köroğlu, Mehmet Yalaz, Mete Akisu, Nilgün Kültürsay

Ege University Faculty fo Medicine, Department of Pediatrics, Division of Neonatology, İzmir, Turkey

ABSTRACT

Aim: In the present study, the relationship between neonatal morbidity and cord vitamin D levels is investigated.

Materials and Methods: Premature infants who were born before 32 weeks of gestation and admitted to our neonatal intensive care unit between January 2014 and January 2015 were included in the study. Vitamin D levels in the cord blood of infants were measured. Serum calcium, phosphorus and alkaline phosphatase levels were recorded in the first 24 hours. All neonates were followed up for neonatal morbidities until discharge.

Results: The mean gestational age of the study subjects was 29.2±2.6 (23-32). The mean vitamin D level was 27.4±19.3 ng/mL (4-76). Fourteen (46.7%) infants had normal vitamin D levels; 2 infants (6.7%) had vitamin D insufficiency (20-30 ng/mL), 14 infants (46.7%) had vitamin D deficiency (<20 ng/mL), and 7 infants had severe vitamin D deficiency (23.3%). In 60% of infants with intrauterine growth restriction had vitamin D deficiency of $p<0.05$. Serum phosphorus levels on the first day of life were significantly lower in infants with vitamin D deficiency ($p<0.001$).

Conclusion: In more than half of the study population vitamin D deficiency was determined. Infants with intrauterine growth restriction had vitamin D deficiency in more than half of the cases. Low levels of phosphorus may be a marker of vitamin D deficiency in the first days of life.

Keywords: Preterm birth, vitamin D, intrauterine growth restriction

Introduction

The importance of vitamin D as a modulator of calcium and bone metabolism is well known (1), and it is also involved in the innate immune system, cell proliferation and neuromuscular functions (2-4). Vitamin D is reported to inhibit the nuclear factor-kappa beta pathway and reduce inflammation in decidua (5). Recently, vitamin D has been suggested to be involved in the pathogenesis of many diseases such as cancer, multiple sclerosis, diabetes and cardiovascular disease via cell proliferation and immune function (6). Vitamin D deficiency in newborns is related to neonatal sepsis and respiratory system infections. Maternal vitamin D deficiency increases the risk of premature delivery, preeclampsia, gestational diabetes mellitus and intrauterine growth restriction (7-9). These perinatal complications trigger preterm delivery and these premature infants have a greater risk of vitamin D deficiency. Studies have shown that vitamin D deficiency is more prominent in the second and third trimesters. The rate of premature delivery is 8-12% in the world and results in fetal morbidity and mortality (10). Considering the wide distribution of vitamin D receptors and its newly suggested roles in many adult diseases, particularly those associated with inflammatory pathways, it may also be involved in neonatal morbidities related to immature immune system and inflammation. Furthermore, early recognition of vitamin D deficiency makes early and appropriate supplementation possible to prevent the increased risk of possible vitamin D related morbidities. Thus, in this study cord blood vitamin D levels were measured

Address for Correspondence
Demet Terek MD, Ege University Faculty fo Medicine, Department of Pediatrics, Division of Neonatology, İzmir, Turkey
Phone: +90 530 692 57 99 E-mail: demet.terek@yahoo.com ORCID ID: orcid.org/0000-0002-0970-6582
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so as to determine the rate of Vitamin D deficiency in very preterm newborns (<32 weeks) and to illuminate its relation with neonatal morbidities.

Materials and Methods

Premature infants with gestational ages below 32 weeks who were born in the University Hospital and admitted to the neonatal intensive care unit NICU between January 2014 and January 2015 were enrolled in the study. Patients with cyanotic heart disease, chromosomal anomalies, and congenital anomalies were excluded from the study. This study was approved by the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval number: 11-12.2/4). The parents provided informed consent for the study.

Assessment of Blood Vitamin D Levels

Vitamin D levels were measured in the cord blood of the infants. Serum calcium, phosphorus and alkaline phosphatase (ALP) levels were measured in the first 24 hours. Serum 25-hydroxyvitamin D3 [25(OH)D3] level lower than 20 ng/mL is defined as vitamin D deficiency. Serum 25(OH)D3 level lower than 10 ng/mL is defined as severe vitamin D deficiency. Serum 25(OH)D3 level between 20-30 ng/mL is defined as insufficient vitamin D (10).

Maternal and Neonatal Demographic and Clinical Data

Detailed antenatal history including maternal age, gestational week, mode of delivery, number of live births, history of preeclampsia, diabetes mellitus, and premature rupture of membranes, was recorded. All the premature infants were prospectively followed for neonatal morbidities (Respiratory Distress syndrome [RDS]), sepsis, pneumonia, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), intraventricular hemorrhage, mortality and the duration of mechanical ventilation. Clinical sepsis is defined as documentation of infection with a serious systemic illness in which non-infectious explanations for the abnormal pathophysiological state are excluded or unlikely. By definition, in early clinical sepsis clinical signs appear in the first 5 days and in late sepsis >5 days (11). RDS is diagnosed clinically with early respiratory distress manifested with cyanosis, grunting, retractions and tachypnea. The diagnosis is confirmed with blood gas analysis and chest X-ray with a classical "ground glass" appearance and air bronchograms (12). BPD is defined according to universal guidelines in infants with prolonged oxygen requirement and accompanying radiological changes (13). NEC is the mucosal ischemic necrosis of the intestines. Staging defined by Schanler et al. (14) is used. Intraventricular bleeding is classified according to Papile classification (15).

Statistical Analysis

SPSS 16.0 (SPSS, Chicago, IL) was used for statistical analysis. The stastitical analyses were performed in Ege University Bioistatistics Unit. Data were expressed as mean and standard deviation. Differences between the two groups were analyzed by Student t-test or Mann-Whitney U test, where appropriate. Pearson test was used to analyze the correlation between variables. p value of <0.05 was accepted as significant.

Results

The mean gestational week of the study population was 29.2±2.6 (23-32), the mean birth weight was 1331±414 (620-2815) grams (Table I). In antenatal history preeclampsia rate was 20% (n=6) and intrauterine growth restriction rate was 16.7% (n=5) (Table I). In clinical follow-up, the rate of RDS was 46.3% (n=14), sepsis 50% (n=15), pneumonia 16.7% (n=5), BPD 25% (n=7), NEC 10% (n=3), intraventricular bleeding 36% (n=11) and mortality was 16.7% (n=5). The mean vitamin D level was 27.4±19.3 ng/mL (4-76). Vitamin D level was normal in 14 cases (46.7%). Vitamin D insufficiency was present in two cases (6.7%) while 14 cases (46.7%) had vitamin D deficiency. Severe vitamin D deficiency was seen in 7 cases (23.3%) (Table II). Gestational age and birth weights of infants with or without vitamin D deficiency were similar . However, intrauterine growth restriction was present in 42% of cases with 25(OH)D level lower than 10 ng/mL. Intrauterine growth restriction was present in 8.7% of cases with 25(OH)D level greater than 10 ng/mL. In 60% of cases with intrauterine growth restriction vitamin D level was ≤20 ng/mL (p<0.05). There was no correlation between vitamin D deficiency and premature rupture of membranes, neonatal sepsis, respiratory distress, NEC, BPD, intraventricular bleeding and mortality. On the first day of life, the mean calcium level was 8.3±0.8 mg/dL. and the mean phosphorus level was 4.6±1.46 mg/dL. In cases with vitamin D deficiency, the mean phosphorus level was significantly lower (p<0.001) (Table III).

Table I. Demographic data

Mean gestational age	30±2.9
Mean birth weight	1335±414
Female/male ratio	12/18
Rate of preeclampsia	6/30 (20%)
Rate of gestational diabetes mellitus	2/30 (6.7%)
Rate of premature rupture of membranes	5/30 (16.6%)
Delivery mode	C section 23/30 vaginal 7/30

Table II. Vitamin D levels of cases

25(OH)D level	Distribution of cases (n/%)
>30 (ng/mL)	14 (46.7)
20-30 (ng/mL)	2 (6.7)
≤20 (ng/mL)	14 (46.7)
≤10 (ng/mL)	7 (23.3)

25(OH)D: 25-hydroxyvitamin D

Table III. Serum calcium, phosphorus and alkaline phosphatase levels in the first 24 hours of life

	Vitamin D >20 ng/mL	Vitamin D ≤20 ng/mL	p value
Mean calcium	8.5±0.7 mg/dL	8.2±0.8 mg/dL	0.44
Mean phosphorus	5.1±0.8 mg/dL	3.3±0.8 mg/dL	0.001
Mean ALP	168±70 IU/L	164±50 IU/L	0.80

ALP: Alkaline phosphatase

Discussion

Vitamin D deficiency is a worldwide problem and yet it is a preventable disease. Umbilical cord vitamin D level is correlated with maternal serum vitamin D level. Also, in fetal and neonatal period vitamin D level correlates with maternal serum level of vitamin D. During pregnancy if the mother has a vitamin D deficiency, fetuses carry a significant risk of vitamin D deficiency. The rate of vitamin D deficiency in premature infants is reported to be 64% in the United States of America, 83% in India, 63.7% in France. In a study from Australia, vitamin D levels in cord blood was <20 ng/mL in 40% of infants (16). There are limited studies on neonatal vitamin D levels in our country; and most data are obtained from studies in children. Ataseven et al. (17) from Middle Black Sea, examined 152 preterms with gestational ages 29-35 weeks. They found severe vitamin D deficiency in 64%. Serum 25(OH)D3 is a very good marker of vitamin D level in the blood. In our study the mean 25(OH)D level was 27.4±19.3 ng/mL (4-76). Vitamin D level was normal in 14 cases (46.7%). Vitamin D insufficiency was present in two cases (6.7%), and vitamin D deficiency was seen in 14 cases (46.7%). Severe vitamin D deficiency was present in 7 cases (23.3%). Burris et al. (18) reported umbilical cord 25(OH)D level of 34 ng/mL in their study including term and preterm infants. In their study 40% of the newborns had vitamin D levels lower than 30 ng/mL and 14.4% had vitamin D levels lower than 20 ng/mL. In the same study population 25% of the newborns born before 32 weeks of gestation had vitamin D levels lower than 20 ng/mL. In our study the mean vitamin D level was lower and vitamin D deficiency rates were higher when compared to Burris study.

In another study the mean vitamin D level in premature infants was 16.3 ng/mL (19). Park et al. (20) found vitamin D level as 10.7±6.4 ng/mL in a study of 278 cases with a mean gestational age of 33±2 weeks. In the cohort of Park et al. (20) 91% of newborn babies have vitamin D deficiency and there is severe vitamin D deficiency in 51%. In our study the mean vitamin D level was higher and vitamin D deficiency rates were lower when compared to the above studies (19,20). In our study, vitamin D levels were not related to gestational age and birth weight. Burris et al. (18) did not see any linear correlation between vitamin D level and gestational week. Park et al. (20) reported insignificant correlation of vitamin D levels with gestational age and birth weight.

We did not observe any correlation of vitamin D levels and the presence of premature rupture of membrane. In our cases with intrauterine growth restriction vitamin D level was ≤20 ng/mL in 60% of cases ($p<0.05$). Low maternal vitamin D levels during pregnancy also have been shown to be associated with increased risk of specific conditions including gestational diabetes, preeclampsia and poor fetal growth (20). Park et al. (20) reported insignificant correlation of vitamin D levels with premature rupture of membranes and preeclampsia, and a small correlation with gestational age. Wei et al. (8,9) reported a higher risk of preterm delivery, preeclampsia, gestational diabetes mellitus in maternal vitamin D deficiency. In our study the striking finding is the lower vitamin D level in the newborns with intrauterine growth restriction. We found no correlation between vitamin D deficiency and neonatal sepsis, respiratory distress, NEC, intraventricular bleeding and mortality. Onwuneme et al. (21) reported no significant statistical correlation between vitamin D level and respiratory distress, NEC, intraventricular bleeding, sepsis and mortality in 94 preterm infants under the gestational age of 32 weeks. But Fettah et al. (22) found significantly increased respiratory distress risk in infants with vitamin D levels lower than 15 ng/mL. In our study, on the first day of life, the mean calcium level was 8.3±0.8 mg/dL and the mean phosphorus level was 4.6±1.46 mg/dL. In cases with vitamin D deficiency, the mean phosphorus level was significantly lower. In similar studies in the literature, serum calcium and phosphorus levels do not change significantly; however, there is prominent increase in ALP levels (20).

Study Limitation

There is not enaught number of cases.

Conclusion

Vitamin D deficiency was present in more than half of the study population. Vitamin D deficiency was encountered more often in intrauterine growth restricted fetuses. The low phosphorus level on the first day of life may be a marker of vitamin D deficiency. More studies are needed with larger populations of premature infants to clarify the complex interactions of vitamin D.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval number: 11-12.2/4).

Informed Consent: The parents provided informed consent for the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Medical Practices: N.K., M.Y., Concept: Ö.A.K., M.A., Design: Ö.K., D.T., M.Y., Data Collection or Processing: D.T., G.Ö., Analysis or Interpretation: D.T., M.Y., Literature Search: D.T., F.E., Writing: N.K., Ö.K., D.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

Severe Metabolic Acidosis and Pulmonary Edema: A Near-Drowning Case

Yasemin Çoban, Mehmet Davutoğlu

Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Intensive Care Unit, Kahramanmaraş, Turkey

ABSTRACT

Drowning is defined as a situation which results in the death of the patient within the first 24 hours, while "near-drowning" refers to all conditions of submersion which does not cause death but brings about morbidity and damaging effects. A twenty-five-month-old boy was found immobile in a bathtub filled with water. The patient was transported to the intensive care unit from the emergency department where he vas ventilated with a bag-mask, then intubated, and diagnosed with respiratory insufficiency, and his respiration was supported by mechanical ventilator. Physical examination of the patient showed that he was hypothermic, not breathing spontaneously, his heart rate was 120/min., blood pressure 100/80 mmHg, he was unconscious, and Glasgow Coma scale was 5. The first blood analysis results were mmol/L. The pulmonary edema regressed, cardiopulmonary hemodynamic returned to normal. Then, at the 48th hour he was weaned from mechanical ventilator support. The patient was discharged from the hospital in good health, without negative cognitive and motor symptoms on the 10th day. The present case report aimed to highlight the importance of basic and advanced life support in cases of near-drowning which happens frequently among children, and to discuss the management of pulmonary edema and other complications.

Keywords: Near-drowning, child, pulmonary edema

Introduction

Drowning is defined as a condition resulting in death due to complete submersion or immersion in water. Near-drowning is used to describe all submersions in water not ending in death in the first 24 hours but with accompanying morbidity, and which may give rise to adverse outcomes. Drownings are particularly common in children under 5 and in young adults (1,2). Asphyxia is responsible for morbidity resulting from near-drowning. The effect on the brain depends on the duration, intensity and timing of hypoxia. Hypoxia lasting for 4-10 minutes causes irreversible damage in the hippocampus, basal ganglia and cortex, while hypoxia lasting a few minutes longer results in persistent coma (3). This report discusses therapeutic methods and complications in the light of the existing literature, in a 25-month-old case of near-drowning presenting with severe metabolic acidosis, severe hypoxemia and pulmonary edema.

Case Report

A 25-month-old boy was found by his family immobile in a trough full of water. It was unclear how long he had been submerged. The patient was ventilated with a balloon mask by the first aid team and brought to our pediatric emergency department. At initial examination, his body temperature was <36 °C, heart rate 120 beat/min, blood pressure 100/80 mmHg, and Glasgow Coma score (GCS) was 5. The pupils were isocoric, bilateral light reflex (+), and deep tendon reflex was normoactive. His respiration was superficial. The patient was intubated and admitted to the pediatric intensive care unit. He was placed on

Address for Correspondence

Yasemin Çoban MD, Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Intensive Care Unit, Kahramanmaraş, Turkey Phone: +90 506 913 99 10 E-mail: yasemincoban83@gmail.com ORCID ID: orcid.org/0000-0002-5283-239X

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mechanical ventilator support at peak inspiratory pressure 15, positive-end expiratory pressure (PEEP) 5, pressure support ventilation (PSV) 7, FiO_2 100%, and respiration rate 25/min in synchronized intermittent mandatory (SIMV)+PS. Arterial blood gas analysis revealed pH 6.9, $PaCO_2$ 38.1 mmHg, PaO_2 54 mmHg, HCO_3: 8 mmol/L, and baz excess (BE) -1.7 mmol/L. Sodium bicarbonate deficit therapy and 0.45% NaCl+5% dextrose fluid were started. At follow-up after 1 hour, arterial blood gas was pH 7.20, $PaCO_2$ 40 mmHg, PaO_2 75 mmHg, HCO_3 17 mmol/L, and BE -8.8 mmol/L. At the 8th hour, pH was 7.49, $PaCO_2$ 16.5 mmHg, PaO_2 137 mmHg, HCO_3 17 mmol/L, BE -10.4 mmol/L, and lactate 30 mg/dL. Blood gases improved gradually and returned to normal limits in 8 hours. The blood count showed Hb 12.4 g/dL, hematocrit 37.4%, leukocytes 27.610 mm^3, and platelets 58.5000 mm^3. According to biochemical examinations, sodium was 132 meq/L, potassium 2.6 meq/L, glucose 132 mg/dL, alkaline phosphatase 29 U/L, aspartate aminotransferase 51 U/L, urea 20 mg/dL, creatinine 0.47 mg/dL, calcium 9.41 mg/dL, and Pediatric Risk of Mortality III score was 22. No findings of hemolysis were observed in peripheral blood smear. Coagulation tests revealed prothrombin time as 14.3 sec., activated partial thromboplastin time 135 sec., and international normalized ratio as 1.23. Fresh frozen plasma replacement was administered, and the coagulation tests gave normal results following the replacement. A loading dose of phenytoin of 20 mg/kg was given due to convulsion during admission, with maintenance of phenobarbital 5 mg/kg. Sedation/analgesia was induced with fentanyl and midazolam infusion. Bilateral, diffuse, homogeneous pulmonary edema was observed at posteroanterior chest X-ray (Figure 1). Control X-ray after 12 hours on invasive mechanical ventilation support showed that expansion had begun in the lungs, and that bilateral homogeneous infiltrations had decreased but still persisted (Figure 2). Clinical and laboratory follow-ups were performed close to the invasive monitor, and the patient was removed from the invasive mechanical ventilator after 48 hours. Cranial computerized tomography performed to exclude cerebral edema was reported as normal.

Suprasternal and intercostal retractions occurred following extubation, and the patient was started on inhaled adrenaline, cold vapor and systematic dexamethasone. The respiratory problems had resolved entirely by the seventh day of hospitalization, no neurological deficit remained, and the patient was removed from intensive care. Cognitive functions were at normal levels for his age at one-month follow-up post-discharge. Written consent was obtained from the patient's parents.

Discussion

Neurological injury occurring as a result of hypoxemia and ischemia is the primary cause of mortality and morbidity in cases of drowning and near-drowning. Aspiration of

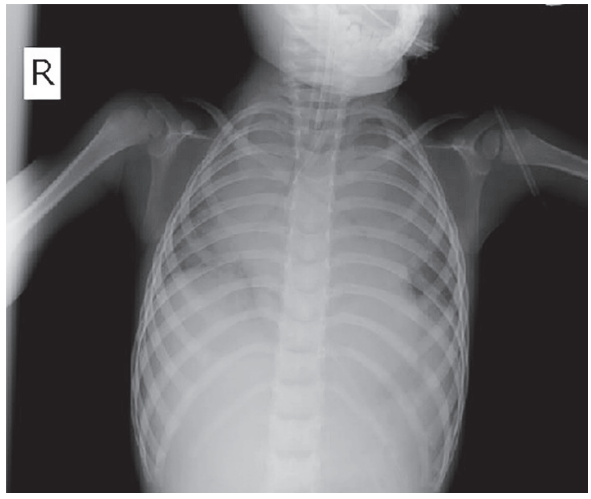

Figure 1. Diffuse, homogeneous pulmonary edema in both lungs in which the heart contours cannot be clearly distinguished. (Appearance 1 h after the near-drowning incident)

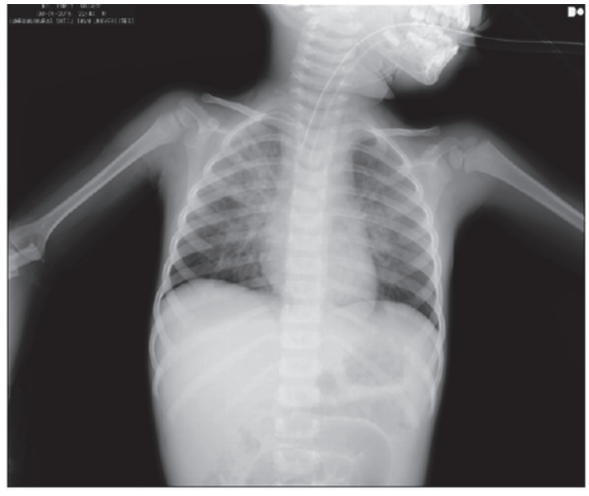

Figure 2. Posteroanterior chest X-ray: The lung is better expanded and the edema has contracted. (Appearance 12 h after the near-drowning incident)

salt or fresh water leads to hypoxemia with the formation of alveolar-capillary oxygen difference. The degree of hypoxia depends on several factors, such as duration of submersion, water temperature, the patient's age, early initiation of advanced life support, and time to admission to the emergency department and intensive care. Previous studies have generally compared prognosis with water temperature and the duration of submersion. Many studies have reported that good outcomes are associated with the duration of submersion and the patient's age (4,5). In one retrospective study, Quan et al. (4) examined 2628 cases of drowning and observed that better outcomes were obtained in drowning lasting up to 10 minutes, at a level of 34% (95% confidence interval 1.01-1.79), in children aged 0-4 years. The authors have emphasized that the outcomes may be poorer in subjects submerged for longer than 10 minutes, and that rescue and resuscitation efforts need to be revised. However,

since durations of submersion depend on witness estimates, comparison with more rational values determining prognosis (such as pH, lactate levels, neuron-specific enolase, plasma glucose levels, and cardiac troponin I) may elicit more reliable findings (6,7).

Studies concerning water temperature have reported inconsistent findings. Tipton and Golden (8) reported that low water temperature was associated with better outcomes, while Quan et al. (4) determined no relation between water temperature and outcome. Our patient was found in water with a temperature above 4 °C. Although the duration of immersion was uncertain, he had drowned in such a way as to rise to the surface of the water. Respiration was superficial when the patient was found, he was not intubated by the first aid team, and he was brought to the emergency department with respiration support via positive pressure mask. Hypoxemia findings, severe metabolic acidosis, bleeding diathesis, convulsion and loss of consciousness were observed on arrival at the emergency department. Pulmonary symptoms may assume various forms in cases of drowning and near-drowning. Patients may be entirely asymptomatic, or may exhibit clinical findings even including pulmonary edema and acute Respiratory Distress syndrome. Pulmonary edema in our case was determined clinically and radiologically (Figure 1). We applied fluid restriction, the amount of fluid to be given being adjusted on the basis of blood pressure, hourly urine output and central venous pressure, after which the patient was started on diuretic therapy. PEEP was applied at a level of 5 cm/H_20 in SIMV+PS mode with conventional mechanical ventilation. Optimal benefit was obtained from PEEP, and the patient was successfully removed from the mechanical ventilator after 48 hours. Ampicillin-sulbactam therapy was initiated due to the patient's being intubated, the fact that the manifestation of pulmonary edema could not be completely differentiated from pneumonia, and because the incident had taken place in a trough used for watering animals. No growth occurred in tracheobronchial aspirate cultures at follow-up, and pneumonia did not develop. This was in agreement with studies showing that drowning in polluted, fresh or salt water does not have an impact on the outcomes (9). Other systemic complications of near-drowning include hypothermia, metabolic acidosis, electrolyte imbalance, hemolytic anemia and hypo- and hypervolemia. Hypothermia is a commonly encountered condition in cases of drowning and near-drowning. It is particularly significant in terms of causing impairment of heart functions. However, rapid-onset hypothermia is also known to have a protective effect on the central nervous system (CNS). We think that hypothermia played a role in our patient's recovery without neurological sequelae. We also think that our patient's being very young, and therefore having good neuronal plasticity, also contributed to his protection against hypo-hyperglycemia, hypo-hypertension and hypo-hyperoxemia. The CNS indisputably undergoes the most significant damage in hypoxemia. Bradycardia, submersion exceeding 10 minutes in duration, GCS being <5, blood glucose level >300 mg/dL and a lactic acid level on the first day of >6 mmol/L are regarded as poor prognostic indicators in cases resulting in death or severe neurological deficit (10). In conclusion, incidents of drowning or near-drowning represent an important cause of hypoxic brain damage frequently seen in the summer months. Since the duration of hypoxemia is an important factor in determining prognosis, basic life support training needs to be given to all individuals responsible for child care in order for them to be able to intervene promptly and appropriately. In addition, advanced life support courses need to be made more available in order to overcome gaps in knowledge and skills on the part of first aid teams performing initial procedures and of all emergency personnel. Care must be taken over fluid electrolyte and the acid-alkali balance through invasive arterial and venous monitoring in intensive care management, and metabolic acidosis must be corrected. PEEP is highly effective, in addition to protective mechanical ventilation strategies, in resolving pulmonary edema in those cases in which it develops.

Ethics

Informed Consent: Informed consent was obtained from the patient's parents.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: M.D., Y.Ç., Design: Y.Ç., M.D., Supervision: M.D.,

Data Collection or Processing: Y.Ç., Analysis or Interpretation: M.D.,Y.Ç., Literature Search: Y.Ç, M.D., Writing:Y.Ç, M.D., Critical Review: M.D.

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Case Report

Congenital Penil Lymphedema in a Preterm Neonate

Şahin Hamilçıkan, Emrah Can

University of Health Sciences, Bağcılar Training and Research Hospital, Clinic of Pediatrics, İstanbul, Turkey

ABSTRACT

Congenital penile lymph edema is a rare anomaly of unknown cause of the lymphatic vessels. Lymphedema is often the shortage of lymphatic collecting ducts, lymphatic hypoplasia, hyperplasia, as a result of aphasia or lymph node fibrosis associated with the pathological development of lymphatic vessels. Lymphedema is generally a permanent condition and surgical treatment is necessary. Here we present the case of a newborn at 26 weeks via caesarean section with congenital penile edema, and no detection of chromosomal anomalies.

Keywords: Preterm, lymphoedema, genital edema

Introduction

Congenital lymphedema is a rare pathology characterized by the abnormal development of the lymph vessels. Although the incidence below age 20 is predicted to be 1.15/100.000, frequency in newborns, especially in preterm neonates is unknown. Lymphedema consists of various lymph vessel pathologies including hypoplasia, hyperplasia, aplasia and lymph node fibrosis, and can be divided into two main groups as acute or chronic lymphedema (1,2). In this article, we present a preterm neonate with congenital penile lymphedema which became notable 3 days after birth and lessened in the following weeks.

Case Report

A neonate weighing 960 grams was delivered by Caesarean section in the 26th gestation week. Patient history revealed no antenatal follow-up. Appearance, Pulse, Grimace, Activity, and Respiration scores were 5 and 8 in the first and fifth minutes of birth respectively. He was admitted to neonatal intensive care unit (NICU) for Respiratory Distress syndrome and started on ampicillin and gentamicin treatment. On the third day of hospitalization, significant penile edema was detected. He had no history of urinary catheterization prior to edema; and urine analysis and protein levels obtained by bag urine collection, urinary system ultrasonography, blood cell count and blood biochemical analysis showed no pathology. On the third day the patient developed a fever of 37.8 degrees but continued to receive the same antibiotic regimen. Acute phase reactants were negative. Despite the fact that initially penile edema was thought to be related to clinical sepsis, persistence in the following days led us to consider differential diagnosis, and the patient was referred to the urology department for urethra related pathologies, to pediatric nephrology for other urinary tract abnormalities, to pediatric surgery and pediatric endocrinology for Turner syndrome, hypothyroidism and related disorders. Cow's milk specific immunoglobulin E (IgE) and egg yolk specific IgE were evaluated after the pediatric allergy consultation and found within normal limits. Provocation test was used to further differentiate cow's milk allergy but no clinical response was observed. Penile venous Doppler ultrasonography showed no pathology but the patient continued to have penoscrotal swelling in the following weeks. Primary lymphedema was considered as a diagnosis of exclusion. When the patient was discharged from NICU at the 33rd week of gestation, he

Address for Correspondence

Emrah Can MD, University of Health Sciences, Bağcılar Training and Research Hospital, Clinic of Pediatrics, İstanbul, Turkey

Phone: +90 532 512 36 06 E-mail: canemrahcan@yahoo.com ORCID ID: orcid.org/0000-0002-2163-6564

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weighed 2000 grams and had no other complaints (Figure 1). During the outpatient follow-up, he was consulted at the genetics department and chromosome analysis revealed no pathology. Tandem mass spectrometry, blood amino acid, and urine organic acid showed no sign of any metabolic diseases. Toxoplasma, others, rubella, cytomegalovirus, herpes screening resulted negative. Cranial ultrasonography and optometry were found normal. Penile edema started to resolve after 4 months and the patient was fully recovered after 6 months of follow-up. Written informed consent from a parent was obtained for this neonate prior to the study.

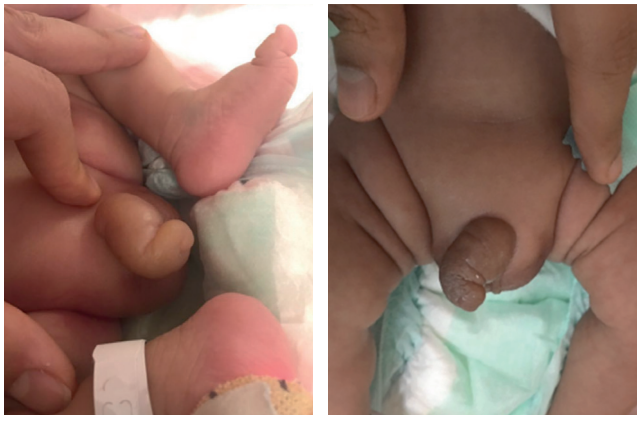

Figure 1. Congenital penil lymphedema in a neonate

Discussion

Congenital lymphedema is an autosomal dominant disorder and constitutes 10-20% of the lymphedemas (3,4). Our case had no history of similar cases, and there was no consanguineous marriage in the family. Congenital lymphedema presents as edema of both extremities after birth and does not usually get worse. Milroy disease is also a cause of congenital lymphedema and it is seen in patients with family history. Patients frequently have edema of the lower extremities that sometimes reach out to the genitalia (5). Our baby showed no sign of lower extremity edema in the early postnatal period. He just had edema in the penile region, starting in the dorsum of the penis and continuing to the glans. He did not show any sign of lower extremity edema in the following days either. The diagnosis of congenital lymphedema is made by family history, especially urinary tract infections and similar cases in the family; and physical examination. There are no specific laboratory tests. The most significant point is to differentiate it from secondary lymphedema, therefore, other system evaluations, abdominal ultrasonography, urinary system evaluation and Doppler ultrasonography of iliac and inferior vena cava should be considered. For cases with edema of the lower extremities, genetic consultation is suggested. In our case, all these workups were performed and they revealed no positive results. Lymphangiogram is suggested for some complicated cases to make a definite diagnosis but application in newborns, especially in preterm neonates, is difficult (6,7). We did not perform lymphangiogram in our case due to technical difficulties and the low success rate in children. Although lymphoscintigraphy has high sensitivity and specificity, we could not perform the test on our patient (5) as he was premature. Differential diagnosis of congenital penile edema are congenital lymphedema related Turner syndrome, Noonan syndrome, trisomy 13, 18 and 21. In our case consultation with the genetics department, and chromosomal analysis showed no pathology. Also, hamartomas in familial benign tuberosclerosis may present with lymphedema (8). Cranial and abdominal ultrasonography were performed on our case and no sign of hamartomas was found. The pathogenesis of primary congenital lymphedema due to congenital hypoplasia, deficiency or absence of superficial lymph system is not fully understood (8). One study revealed that the lymphatic system continued to develop after birth (4). From this point of view, it may be stated that idiopathic penoscrotal edema and congenital penile lymphedema are the same entities. Our case also promotes this finding as symptoms began to regress in the 4^{th} month and deteriorated in the 6^{th}. No specific treatment is suggested for the cure of congenital lymphedema. The first and foremost step should be to prevent the progression of the lymph flow by conservative approaches. Appropriate treatment options are compression therapy and elevation. In severe cases abiding for a long period of time or with extra growth or dysfunction, surgery is the treatment of choice (5) although it has been suggested to evaluate each case for operation time and surgery technique (4,5). In our case, surgery was not the first choice of treatment due to the prematurity of the baby, and the good response to conservative therapy. In conclusion, differential diagnosis of congenital lymphedema in newborns with penile edema should be kept in mind and careful evaluation should be done, especially in premature neonates.

Ethics

Informed Consent: Written informed consent from a parent was obtained for this neonate prior to the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.C., Ş.H., Concept: E.C., Design: E.C., Data Collection or Processing: E.C., Ş.H., Analysis or Interpretation: E.C., Ş.H., Literature Search: Ş.H., Writing: E.C., Ş.H.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

Early-Onset Isolated Bilateral Pheochromocytoma As a Major Clinical Manifestation of von-Hippel Lindau Syndrome Type 2C

Şezer Acar[1], Hale Tuhan[1], Korcan Demir[1], Ayça Aykut[2], Asude Durmaz[2], Ünal Utku Karaarslan[3], Gözde İnci[4], Oğuz Ateş[5] Ece Böber[1], Ayhan Abacı[1]

[1]*Dokuz Eylül University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Endocrinology, İzmir, Turkey*
[2]*Ege University Faculty of Medicine, Department of Medical Genetics, İzmir, Turkey*
[3]*Dokuz Eylül University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Intensive Care Unit, İzmir, Turkey*
[4]*Dokuz Eylül University Faculty of Medicine, Department of Pediatrics, İzmir, Turkey*
[5]*Dokuz Eylül University Faculty of Medicine, Department of Pediatric Surgery, İzmir, Turkey*

ABSTRACT

Pheochromocytoma is a rare disease that is characterized by the increased production and secretion of catecholamines from the adrenal medulla. The disease is autosomal dominant, and frequently sporadic and unilateral. Pheochromocytoma, which is diagnosed during childhood, mostly arises as a part of cancer susceptibility syndromes. Among these syndromes, von-Hippel Lindau (VHL) syndrome is dominantly inherited, and is frequently identified in childhood pheochromocytoma. VHL syndrome is clinically characterized with hemangioblastomas of the central nervous system and retina, renal cell carcinoma, and pheochromocytoma, and has been demonstrated to have a strong genotype-phenotype correlation. In this case report, we presented an 11-year-old male who was found to have early-onset isolated bilateral pheochromocytoma and V84L mutation in VHL. We aimed to emphasize that this rarely reported mutation is associated with VHL Type 2C that classically manifests with early-onset isolated bilateral pheochromocytoma.

Keywords: Pheochromocytoma, von-Hippel Lindau syndrome, hemangioblastoma

Introduction

Pheochromocytoma is a rare neoplasm arising from chromaffin cells in the adrenal medulla and is characterized by increased catecholamine synthesis and release. The typical clinical manifestations are headache, excessive sweating (diaphoresis), palpitation, fatigue, and weight loss. The most important physical examination finding is hypertension, which is paroxysmal in half of the cases during childhood (1). Although pheochromocytoma can occur at any age, it most frequently emerges during the 4th and 5th decade of life (2). Moreover, 20% of these cases are detected in childhood and the mean age at diagnosis is 11.0 years (3). The disease is frequently sporadic and unilateral, 10 % is bilateral and 10 % familial (4). Pheochromocytoma can be seen as a component of cancer susceptibility syndromes such as multiple endocrine neoplasia (MEN) Types 2A and 2B (*RET* mutation), von-Hippel Lindau syndrome (VHL mutation), neurofibromatosis Type 1 (*NF1* mutation) and Familial Paraganglioma syndromes (*SDHA, SDHB, SDHC, SDHD* mutations) (5,6). Moreover, in most of the pheochromocytoma cases younger than 18 years of age, it has been reported to have genetic mutations in one of these tumor susceptibility genes (2). Therefore, in contrast to the adult cases, it is noteworthy to screen for genetic causes in cases diagnosed with pheochromocytoma, especially during childhood (2,6). Von-

Address for Correspondence
Ayhan Abacı MD, Dokuz Eylül University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Endocrinology, İzmir, Turkey
Phone: +90 232 412 60 76 E-mail: ayhanabaci@gmail.com ORCID ID: orcid.org/0000-0002-1812-0321
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Hippel Lindau (VHL) syndrome is a rare autosomal dominant disease and is characterized by the presence of benign and/or malign tumors in various tissues and organs such as the central nervous system and retinal hemangioblastoma, pheochromocytoma, renal cyst, and renal cell carcinoma (6,7). The association between VHL and pheochromocytoma was first described in 1964 (7). The incidence of VHL syndrome is estimated to be 1 in 36.000 live births (1). Pheochromocytoma was reported to occur in 20-30% of cases with *VHL* syndrome, and moreover, 40% of these cases were reported to have bilateral pheochromocytoma (7). A well-defined genotype-phenotype correlation between specific *VHL* mutations and clinical presentation has been established (6). Furthermore, VHL syndrome is classified into two groups according to the absence (Type 1) and presence (Type 2) of pheochromocytoma (6). Type 2 is also divided into 3 subgroups, and that isolated unilateral or bilateral pheochromocytoma with missense mutations in the VHL is classified as VHL Type 2C (6). In this case report, we aimed to present a case of VHL Type 2C who presented with isolated bilateral pheochromocytoma and who was identified through a sporadic missense mutation in the VHL.

Case Report

An 11-year-old boy was admitted to our clinic due to headache, fatigue, double vision (diplopia), night sweats, palpitation, and redness or flushing of the skin around the cheeks. He was born via normal spontaneous vaginal delivery at term with a weight of 3600 gr. It was learned from his medical history that he had undergone acute appendicitis surgery four years before. His healthy parents were not related, and family history was not remarkable. On his physical examination, his weight was 27.1 kg [(-1.7 standard deviation score (SDS)], height 135 cm (-1.2 SDS), body mass index was 14.1 kg/m^2 (-1.2 SDS). His blood pressure was 182/125 mmHg (95th percentile 118/78 mmHg, 99th percentile 125/86 mmHg), and heart rate 119/min. There was no hypo-hyperpigmentation, facial dysmorphology or any extremity anomalies. The testis volume was bilaterally 4 mL, and there was no pubic or axillary hair. Laboratory analyses revealed normal liver-kidney function tests, ion profiles, and thyroid function tests. Bilateral papillary edema was detected by the ophthalmologist. Abdominal ultrasonography (USG) showed a 3x3 cm hypoechoic mass on the right adrenal gland, and normal left adrenal gland. Abdominal magnetic resonance imaging (MRI) revealed a 4 cm solid mass on the right adrenal gland and a 2 cm solid mass on the left adrenal gland. Positron emission tomography imaging with a somatostatin analogue of gallium-68 labeled somatostatin [DOTA-D-Phe-Tyr3-octreotide (DOTA-TATE)] demonstrated no other pathologic uptake except bilateral adrenal masses. Epinephrine, norepinephrine, and normetanephrine levels in the serum, and normetanephrine levels in 24 hour urinary excretion were found to be high (Table I). Thyroid USG and renovascular doppler USG were normal, echocardiographic examination revealed mild left ventricular hypertrophy. Cranial and spinal MRI were normal. Clinical, laboratory and radiological findings were suggestive of bilateral pheochromocytoma. In the pre-operative period, due to its not being available in our country, an attempt was made to provide phenoxybenzamine from abroad for the treatment of hypertension. Firstly, we tried to treat the patient with selective alpha-1 blocker (doxazosin 2 mg/day) and calcium channel blocker (nifedipine 30 mg/day). On follow-up, because of the persistence of high blood pressure, the doses of the drugs were increased to 3 mg/day for doxazosin, 90 mg/day for nifedipine, and phenoxybenzamine 2x5 mg/day was added. With this treatment, we successfully controlled his high blood pressure. Laparoscopic bilateral adrenalectomy was performed following appropriate pre-operative preparations (fluid infusion, methylprednisolone equivalent to hydrocortisone 100 mg/m 2/day just prior to surgery). In the intraoperative period, magnesium sulphate (50 mg/kg as loading dose and 15 mg/kg/hour as maintenance dose) was administered to prevent blood pressure elevation. During the operation, the patient did not develop hypertension, and the surgery was completed without any complications. On the postoperative fourth day, hydrocortisone treatment was replaced by oral maintenance dose (10 mg/m^2/day), and fludrocortisone (0.1 mg/day) was added. Immunohistochemical (chromogranin A and synaptophysin positive) and pathologic evaluations confirmed the diagnosis of bilateral pheochromocytoma. In the genetic analysis, no mutation was detected in the *RET* gene. However, a heterozygous *V84L* (c.250G>T, V84L) mutation in the *VHL* gene, which was previously reported in four families, was identified. Genetic analyses of the mother, father and the brother revealed no *VHL* mutation. In the further investigations regarding benign or malign tumors associated with *VHL* syndrome, no hemangioblastomas of the central

Table I. Levels of catecholamine and its metabolites in the serum and 24 hour urine

	Parameter (unit)	Value	Normal range
Serum	Metanephrine (nmol/L)	0.13	0.08-0.51
	Normetanephrine (nmol/L)	19.78	0.12-1.18
	Epinephrine (pg/mL)	109.5	0-60
	Norepinephrine (pg/mL)	>14000	120-680
Urine	Creatinine (g/day)	0.68	0.30-0.80
	Metanephrine (g/day)	157.3	59-188
	Metanephrine / Creatinine ratio (g/g creatinine)	232.3	41-209
	Normetanephrine (g/day)	10862.2	84-422
	Normetanephrine / Creatinine ratio (µg/g creatinine)	16038.6	53-413
	Vanillylmandelic acid (mg/day)	218.8	1.8-6.7
	5-hydroxyindoleacetic acid (mg/day)	3.82	0.5-8.2

nervous system or retina, cystic or solid structures in the liver, pancreas, and kidney were detected.

Consent form was obtained from the parents of the patient for this case presentation.

Discussion

The typical symptoms (headache, palpitations, sweating), elevation of serum and urine catecholamines and their metabolites, hypertension, solid masses detected in both adrenal glands suggested the diagnosis of pheochromocytoma. Bilateral pheochromocytoma was confirmed by immunohistochemical and histological evaluations performed after surgery. Bilateral pheochromocytoma in childhood can occur as part of familial tumor syndromes such as MEN 2A/2B, neurofibromatosis Type 1, familial paraganglioma syndromes, and VHL syndrome (2,6,8). In a study conducted by Baush et al. (2), genetic analyses of 177 pheochromocytoma cases, who were within the range of 4-17 years and 19% of whom were sporadic and 33% were bilateral pheochromocytoma, were performed. Various mutations regarding Familial Tumor syndromes associated with pheochromocytoma in 130 patients (80%) were reported. Furthermore, 93 of 130 (53%) were *VHL* mutation as the most frequent genetic type. Of these cases with *VHL* mutations, 36 cases (39%) were reported as having bilateral pheochromocytoma. In another study, Neuman et al. (5) performed genetic analyses (VHL, RET, SDHD, SDHB) of 271 pheochromocytoma cases without family history and syndromic features, and detected various genetic mutations in 66 cases (24%). Among the cases in which mutations were detected, the most common genetic type was *VHL* (30 cases, 45%). Moreover, 20 cases (66.7%) diagnosed with *VHL* mutation were under 18 years of age. In the same study, it was emphasized that *VHL* mutations were more frequent especially in children and adolescents with isolated pheochromocytoma. Therefore, genetic causes should be investigated in cases of sporadic pheochromocytoma diagnosed in childhood. In our patient, who had bilateral pheochromocytoma at an early age, genetic studies regarding Familial Tumor Susceptibility syndromes were performed, and a de novo missense mutation (c.250G>T, V84L) was detected in the *VHL* gene, which was previously described in four families. There are two different subtypes of VHL syndrome (Table II). *VHL* Type 1 is characterized by tumor structures such as central nervous system or retinal hemangioblastoma, but no pheochromocytoma. VHL type 2 is divided into three subgroups, and unlike VHL Type 1, is accompanied by pheochromocytoma. In Type 2B, different from Type 2A, renal cell carcinoma frequently occurs. Type 2C is mostly presented with isolated unilateral or bilateral pheochromocytoma (6,8). In some studies, the genotype-phenotype correlation of the subtypes of VHL syndrome has been tried to be established (8,9). While missense mutations are frequently detected in VHL Type 2, missense and nonsense mutations are more frequent in VHL Type 1 (9) (Table II). A missense *VHL* mutation (c.250G>T) was detected in our patient presented with isolated bilateral pheochromocytoma. As a result of this mutation, valine amino acid at position 84 was replaced with leucine. The *VHL* mutation (c.250G>T, V84L), which we identified in our case, was previously reported in 4 families (8 cases) and associated with isolated bilateral pheochromocytoma (6,10). All of these cases were reported to develop isolated bilateral pheochromocytoma between the ages of 4 and 23 but on follow-up, in one of these cases, a spinal hemangioblastoma was detected at the age of 54. However, the relationship between the spinal hemangioblastoma that developed 23 years later and VHL syndrome has not been clearly elucidated and it has been suggested that it may be coincidental. In our case, cranio-spinal imaging and retinal evaluation were normal. Taken together, the clinical and genetic results of our patient indicated the diagnosis of VHL Type 2C. Although neoplasia is not expected in VHL Type 2C except for pheochromocytoma, we planned to perform radiological screenings at regular intervals, since a case has been reported to develop spinal hemangioblastoma 21 years after bilateral pheochromocytoma was first detected. It is suggested to start preparations for surgical procedure rapidly after confirming the diagnosis of pheochromocytoma. Medical treatment should be given for at least 10-14 days prior to surgery to restore normal high blood pressure, which is caused by catecholamines (11). There are different treatment approaches for hypertension in pheochromocytoma. The most common approach in the world is to start treatment with alpha-receptor blockers (11). However, if hypertension cannot be controlled, beta-receptor blocker, calcium channel blocker should be considered (11). We first started our treatment with doxazosin, an alpha blocker. The blood pressure could not be normalized with this treatment, so we added nifedipine, a calcium channel blocker, and phenoxybenzamine, as a result of which we managed to control the hypertension. In conclusion, VHL syndrome should be considered in the differential diagnosis of childhood sporadic pheochromocytoma. It is important

Table II. Von-Hippel Lindau syndrome subtypes and genotype-phenotype correlation

VHL type	*VHL* mutation type	Retinal HB	CNS HB	RCC	PCC
1	Missense, insertion, splice site, nonsense, microdeletion, wide deletion	+	+	+	-
2A	Missense	+	+	-	+
2B	Missense	+	+	+	+
2C	Missense	-	-	-	+

VHL: Von-Hippel Lindau, HB: Hemangioblastoma, CNS: Central nervous system, RCC: Renal cell carcinoma, PCC: Pheochromocytoma

to investigate the pheochromocytoma cases diagnosed in childhood regarding genetic causes of tumor susceptibility to be able to ensure a more accurate follow-up of the patient, and to give appropriate genetic counseling.

Ethics

Informed Consent: Consent form was obtained from the parents of the patient for this case presentation.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O. A., K.D., A.A., Concept: S.A., A.A., K.D., Design: U.K., E.B., H.T., Genetic Analysis: A.A., A.D., Data Collection or Processing: G.İ., S.A., A.P., Analysis or Interpretation: E.B., O.A., A.A., A.A., Literature Search: G.İ., H.T., A.P., A.D., Writing: S.A., A.A., K.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

Lip and Face Edema Due to Face Presentation

Hülya Özdemir[1], Merve Öztürk[2], Hülya Bilgen[1], Eren Özek[1]

[1]*Marmara University Faculty of Medicine, Department of Pediatrics, Division of Neonatology, İstanbul, Turkey*
[2]*Marmara University Faculty of Medicine, Department of Pediatrics, İstanbul, Turkey*

ABSTRACT

A 3100 g male appropriate for gestational age baby was born at 40 weeks to a healthy mother by normal spontaneous vaginal delivery. Apgar scores were 9 and 10 at the 1st and 5th minutes, respectively. Physical examination of the infant's respiratory system, cardiovascular system and his abdominal examination were normal; neurological examination revealed no abnormality. Suspicious syndromic facial appearance with modarete edema at the baby's lips and face was evident and he had bruising on the left nasolabial groove and on both cheeks. We aimed to emphasize the fact that facial edema due to soft tissue trauma seen in newborns born with face presentation may be misinterpreted as a sign of a syndrome. However, careful anamnesis, thorough physical examination, and close follow-up could ensure the diagnosis of birth trauma.

Keywords: Birth trauma, face presentation, newborn

Introduction

Neonatal facial birth injuries are easily recognizable, but they are the most under-reported form of birth injuries. Newborn infants with face presentation usually have severe facial edema, facial bruising or ecchymosis. Anything that delays or prevents flexion such as fetal anomalies, contracted pelvis, fetopelvic disproportion or cord around the neck can contribute to face presentation (1). Repeated vaginal examination to assess the presenting part and the progress of labor may lead to bruises in the face as well as damage to the eyes. We aimed to emphasize the fact that facial edema due to soft tissue trauma seen in newborns born with face presentation may be misinterpreted as a sign of a syndrome. However, careful anamnesis, thorough physical examination, and close follow-up could ensure the diagnosis of birth trauma.

Case Report

A 3100 g male appropriate for gestational age baby was born at 40 weeks to a healthy mother by normal spontaneous vaginal delivery. Apgar scores were 9 and 10 at the 1st and 5th minutes, respectively. His parents were healthy and had no consanguinity. The mother did not attend routine prenatal care on a regular basis and did not receive any medication during pregnancy. The weight of the infant was 3100 g (10-50 percentile), height was 48 cm (10-50 percentile), and head circumference was 35 cm (50-90 percentile). Physical examination of the infant's respiratory system, cardiovascular system, and his abdominal examination were normal, as was his neurological examination. Suspicious syndromic facial appearance with moderate edema at the baby's lips and face was evident and he had bruising on the left nasolabial groove and on both cheeks (Figure 1). No accompanying lesions were observed in the mouth. The baby was breastfed without any problem after delivery. Edema completely resolved about four hours after birth (Figure 2). Written informed consent was obtained from the patient's parents for the publication of this case report.

Discussion

Birth trauma is the physical damage of the baby during the birth process due to the exposition of mechanical effects (2). Birth traumas are less reported in cesarean

Address for Correspondence
Hülya Özdemir MD, Marmara University Faculty of Medicine, Department of Pediatrics, Division of Neonatology, İstanbul, Turkey
Phone: +90 533 351 83 45 E-mail: hulyazeynep@yahoo.com ORCID ID: orcid.org/0000-0002-4867-2514
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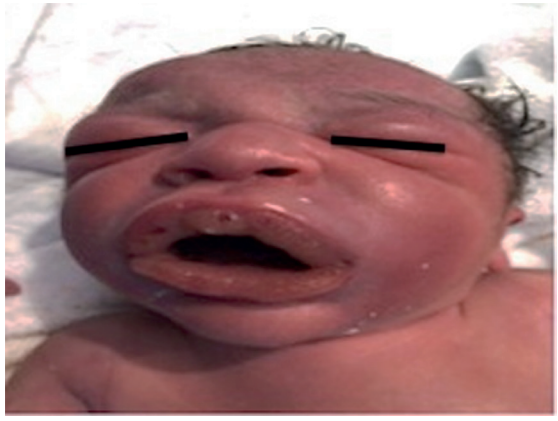

Figure 1. Infant's face appearence at the first hour of life

Figure 2. Infant's face appearence at the fourth hour of life

deliveries (3). The incidence of birth trauma has decreased with the improvements in obstetric care and prenatal diagnosis; and birth trauma frequency has been reported as 2% in vaginal and 1.1% in cesarean deliveries (4,5). Risk factors include macrosomia, preterm delivery, prolonged labor, maternal obesity, fetal presentation anomalies and operative delivery (forceps or vacuum) (6). The most common type of birth trauma is soft tissue trauma, which can be seen as ecchymosis on the skin, petechia, laceration and subcutaneous fat necrosis (7). Genital edema and ecchymosis can be seen on breech presentation. Laceration is the most commonly seen soft tissue trauma in cesarean delivery (3).

The prevalence of face and brow presentation has been reported as 0.14% to 0.54% in deliveries (8). Face presentation is associated with multiparity, macrosomia, cephalopelvic disproportion, prematurity, polyhydramnios, and fetal anomalies (such as anencephaly or cervical mass) (9). Newborn infants with face presentation usually have severe facial edema, facial bruising or ecchymosis. They mostly recover within 24 to 48 hours. Eyelid swelling and ulceration, retinal or subconjunctival hemorrhage may occur as a result of nasal septum dislocation and ocular trauma may occur due to the pressure of the mother's symphysis pubis or sacral promontorium on the baby's face (1,9). Severe respiratory distress has been reported in certain cases due to a swollen tongue (10). In our case, significant facial and labial swelling was observed as well as ecchymosis on cheeks due to facial presentation, and they recovered spontaneously within hours. There were no findings in other parts of the body related to birth trauma. In conclusion, we aimed to emphasize the fact that facial edema due to soft tissue trauma seen in newborns born with face presentation may be misinterpreted as a sign of a syndrome. However, with careful anamnesis, thorough physical examination, and close follow-up it would be possible to make a certain diagnosis of birth trauma.

Ethics

Informed Consent: Written informed consent was obtained from the patient's parents for the publication of this case report.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Medical Practices: M.Ö., H.Ö., Data Collection or Processing: H.Ö., M.Ö., H.B., Analysis or Interpretation: H.Ö., M.Ö., H.B., E.Ö., Literature Search: H.Ö., M.Ö., H.B., Writing: H.Ö., H.B.

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Case Report

Nasal heterotopy in a Newborn Infant: A Case Report

Tuğba Barsan Kaya[1], Ayşe Aydan Köse[2], Ayşe Neslihan Tekin[1]

[1]*Eskişehir Osmangazi University Faculty of Medicine, Department of Neonatology, Eskişehir, Turkey*
[2]*Eskişehir Osmangazi University Faculty of Medicine, Department of Plastic Reconstructive Aesthetic Surgery, Eskişehir, Turkey*

ABSTRACT
Glial heterotopias are rare, congenital, benign, midline, non-teratomatous extracranial glial tissues which are mostly present in the nose and may masquerade as encephalocele or dermoid cyst. These masses appear to share a similar embryogenic origin. Herein, we present a neonatal nasal glioma on the nasal root and glabella area. Although rare, because of their potential to connect to the central nervous system, these disorders are clinically important.
Keywords: Glial tissue, heterotopy, newborn

Introduction

Glial heterotopy is a midline, congenital mass located in the nose, which contains mature glial tissue. Although the incidence is not fully known, taking reported cases into consideration, it has been reported as 1:20.000-40.000 (1,2). Depending on the location, it may be extra nasal, nasal or mixed type. Other rare locations of heterotopic brain tissue may be the lips, tongue, within the scalp, nasopharynx or oropharynx. Encephalocele from midline defects and embryonic origin nasal glioma are similar and are related to the abnormal partition of the ectoderm and neuroectoderm during the development of the nose (2). Diagnosis is made through histopathological evaluation by the removal of the mass with excisional biopsy. Differentiation of nasal glioma from encephalocele cannot be made with histopathological examination. The most important feature of glial heterotopy is that there is no intracranial connection of the mass. It is important to make a clear diagnosis because of the risk of the mass involving functional brain tissue. Although midline located masses of the nose are rarely seen, we presented the case of a newborn infant with nasal glioma to emphasize the significant details of diagnosis and treatment.

Case Report

A female infant weighing 1120 gram, of 26 weeks six days gestation according to the last menstrual cycle was delivered to a 31-year old mother as the 3rd live birth of 5 pregnancies. No fetal anomaly was detected during the prenatal follow-up, and no nasal mass was reported on prenatal ultrasound. Her Apgar score was 7-8 at 1st and 10th minutes respectively. The infant had findings of respiratory distress, so was admitted to the neonatal intensive care unit. In the physical examination, a non-pulsatile mass was seen of polypoid structure with regular borders, located on the midline towards the left with a wide base adjacent to the nasal root (Figure 1a, b). No accompanying malformation was determined. Laboratory investigations revealed no hypothalamic dysfunction. On radiological examination, cranial tomography showed a mass of soft tissue density with no accompanying bone defect, and no extension to the intracranial or the orbital region, and not creating an obstruction in the nasal cavity. On contrast magnetic resonance imaging, a heterogeneous, hypointense appearance was observed on T1 and T2-weighted images and was evaluated as a mass with a mild level of heterogeneous contrast (Figure 2). The material removed with excisional

Address for Correspondence
Tuğba Barsan Kaya MD, Eskişehir Osmangazi University Faculty of Medicine, Department of Neonatology, Eskişehir, Turkey
Phone: +90 506 713 79 30 E-mail: tugbarsan@hotmail.com ORCID ID: orcid.org/0000-0003-0698-1850
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biopsy was identified as a piece of cutaneous with hair and subcutaneous tissue of polypoid structure 4x3x2.4 cm on a base 2.5x2.8 cm. Immunohistochemically it was evaluated as glial heterotopia with (+) glial fibrillary acidic protein. The postoperative appearance of the case is seen in Figure 3. The patient was followed-up in neonatal intensive care unit because of being 3 months premature. Informed consent was obtained from the patient's parents.

Discussion

Glial heterotopy is defined as the congenital abnormal location of mature glial tissue in an area outside the central nervous system without intercranial extension. This terminology is not appropriate as it does not include neoplasm or tumoral tissue. By definition, it is a special type of choristoma. It is not a teratoma structure containing ectoderm, endoderm, and mesoderm layers. The dura, pia and arachnoid of the brain tissue and/or leptomeninges that are defined as a bone defect with herniation continuing to the cranial cavity are clearly separated from the surrounding encephalocele (1). There may be erosion and deformity in the adjacent bone and frequently accompanying hypertelorism. Clinically, lesions may be externally adjacent to the nose (60%), in the nasal cavity (30%) or both areas (10%). Typically it is congenital or develops within the first two years (3,4). Therefore, as in the current case, diagnosis is often made in the neonatal period, but occasionally, the diagnosis of those with intranasal location may be made in adulthood. Other rare locations for heterotopic brain tissue are the lips, the tongue, inside the scalp, the nasopharynx, and the oropharynx. Although rare, they are important because of their potential relationship with the central nervous system (5). The actual incidence is not known, but on the basis of reported cases, it has been stated to be 1:20.000-40.000 (1,2). Family history has not been defined. There have been reports of cases with the combination of corpus callosum agenesis and cleft palate (6,7). Patients present in the early stage of life (often at birth or in the first months) with a subcutaneous nodule in the nose or polypoid mass in the nasal cavity. In patients with an intranasal mass, non-specific findings of nasal obstruction, chronic rhinosinusitis, otitis or allergic symptoms may be seen. If there is accompanying leakage of cerebrospinal fluid, there should be focus on encephalocele (5). A reddish colour in the physical examination of those with extranasal location could be telangiectasia, and those that are non-pulsatile with a covering of skin are often slow-growing polypoid structure masses. In lesions with insufficient blood supply, reactive changes, local calcifications, and ependymal type cystic degeneration may be seen. The masses with intranasal location are on the lateral wall of the nose. Before diagnosing a nasal polyp in unilateral intranasal polypoid masses in particular, detailed tests must be applied. In the current patient, the lesion grew within days, and necrotic changes were seen on the surface. Histologically it was fibrovascular soft tissue containing mature glial cells (astrocytes and oligodendrocytes). Multinuclear giant cells are often seen. In 10-60% of case series, neuron mass is seen. A low level of oxygen in the mass and insufficient neuroectoderm

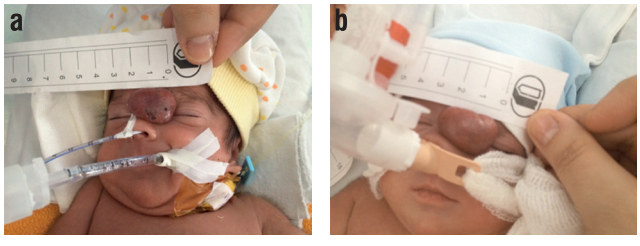

Figure 1. a) The pre-operative apperance of glial heterotopy; a polypoid structure with regular borders, located on the midline mass, b) The pre-operative apperance of glial heterotopy; a polypoid structure with regular borders, located on the midline mass

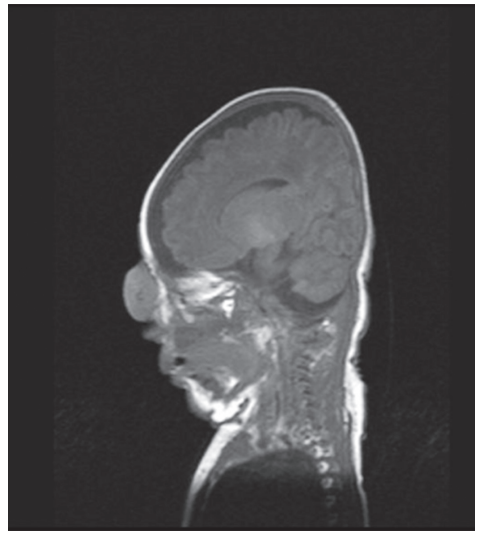

Figure 2. Heterogeneous, hypointense lesion on T1 and T2-weighted magnetic resonance imaging image

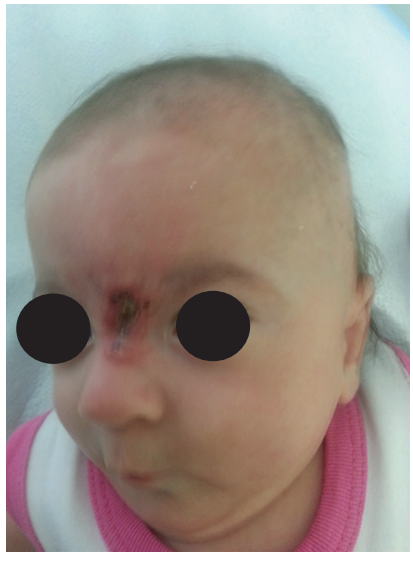

Figure 3. Post-operative apperance of the patient

development cause a low neuron content. Sections prepared for pathological examination may not contain the glial component, and staining with only haematoxylin eosin may not yield information. In suspected cases of glial heterotopy, special staining and immunohistochemical evaluation is necessary. S-100 protein together with Masson Trichrome staining and glial fibril acid staining are important techniques in revealing neurological tissue in fibrotic tissue in particular, and in confirming the diagnosis. In the current case, the diagnosis was confirmed by neuronal tissue showing in glial fibrillary acid staining in the removed mass. Neuron-specific enolase is another stain that can be used (8). Differentiation of glial heterotopy and encephalocele cannot be made with pathological examination. No connection of glial heterotopy with the central nervous system is the most important feature in differentiating it from encephalocele (9). A connection with the central nervous system can be revealed with imaging methods or during surgical procedures. Microscopic invasion, mitotic findings or metastases have not been reported (10,11). Recurrence occurs when the primary lesion could not be fully excised and this has been determined in 4-10% of cases (12). Unlike surgical approaches, evaluation with imaging methods is necessary for the differentiation before the excision procedure of the mass. While tomography gives information related to the defect in the bone structure in particular, magnetic resonance imaging shows soft tissue and intracranial connection. The biopsy and aspiration of pediatric nasal masses are contra-indicated because of the high risk of meningitis and potential damage to functional brain tissue associated with encephalocele. Complete surgical excision is a curative treatment for glial heterotopy (3).

In conclusion, as nasal glioma has the same embryonic root origin, it may be confused with encephalocele and dermoid cysts. Nasal glioma must be carefully evaluated, showing that there is no intracranial connection and that it is ectopic tissue, not herniation tissue. Patients with cerebrospinal fluid leakage during surgical procedures must be re-evaluated. The case presented here is of a rarely seen nasal glioma as a midline defect of the nose which could be confused with encephalocele.

Ethics

Informed Consent: Informed consent was obtained from the patient's parents.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A.K., Concept: A.A.K., T.B.K., Design: A.N.T., Data Collection or Processing: A.A.K., Analysis or Interpretation: A.N.T., Literature Search: T.B.K., Writing: T.B.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

Persistent Hypertransaminasemia Uncovered Occult Limb-Girdle-Muscle Dystrophy-Type-2C in a Saudi Child

Naglaa M. Kamal[1,2], Hamed A. Alghamdi[2], Abdulrahman Halabi[2], Abdullah O. Alharbi[2], Muhammad Rafique[2], Kamel Abidi[3], Mortada H.H. El-Shabrawi[1], Ayman E. Eskander[1], Hala Mansour[1], Laila M. Sherief[4]

[1]*Cairo University Faculty of Medicine, Department of Pediatric Hepatology, Cairo, Egypt*
[2]*Alhada Armed Forces Hospital, Department of Pediatrics, Taif, Saudi Arabia*
[3]*Tunis Al Manar University Faculty of Medicine, Department of Nephropediatric, Tunis, Tunisia*
[4]*Zagazig University Faculty of Medicine, Department of Pediatrics, Zagazig, Egypt*

ABSTRACT

An asymptomatic 4.5 years-old Saudi girl was referred to the pediatric hepatology service with presumed liver disease because of the persistently elevated transaminases which were discovered accidently during routine laboratory workup. Alanine aminotransferase was 128 IU/L and aspartate aminotransferase was 143 IU/L. Subsequent investigations in the hepatology clinic revealed normal hepatic workup. Muscle related work up revealed increased creatine phosphokinase, abnormal electromyography and motor nerve conduction. Muscle biopsy was suggestive of early stage muscular dystrophy, and analyses were compatible with limb-girdle-muscle-disease Type 2C. Further confirmation was reached by molecular genetic testing. This case demonstrates that increased transaminases do not always suggest liver disease, and occult muscle disease should always be taken into account while investigating patients with unexplained persistent hypertransaminasemia.

Keywords: Aminotransferases, children, creatine phosphokinase, myopathy

Introduction

It is well known that prolonged elevation of aminotransferases (ATs) is often suggestive of acute and chronic hepatic diseases (1). By their presence in various cells, especially hepatocytes, cardiac and skeletal myocytes, the rising of aspartate aminotransferase (AST) level is often attributed to a wide spectrum of clinical disorders. In contrast, the elevation of alanine aminotransferase (ALT) is known as a specific indicator of liver necrosis (2). However, in the absence of hepatic etiology more investigations are required to confirm muscular dystrophy, especially in patients with prolonged elevation of ATs. So, the coincidental finding of elevated ALT/AST may be the presenting sign of muscle disease in many children, and provides an opportunity for early diagnosis. Hence, early creatine phosphokinase (CPK) testing may provide the clue to the diagnosis of occult muscle disease in children with unexplained anicteric hypertransaminasemia (3).

Case Report

A 4.5 years old girl was examined by the general pediatrician because of upper respiratory tract infection. Routine blood analysis showed persistently elevated serum ALT concentrations. A hepatic problem was suspected and the patient was referred to the pediatric hepatology and gastroenterology clinic for further investigation of liver

Address for Correspondence
Naglaa M. Kamal MD, Cairo University Faculty of Medicine, Department of Pediatric Hepatology, Cairo, Egypt
Phone: +09 665 655 800 81 E-mail: nagla.kamal@kasralainy.edu.eg ORCID ID: orcid.org/0000-0002-8535-3838
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disease, which revealed normal serum bilirubin, gamma glutamyltranspeptidase, alkaline phosphate, albumin and prothrombin time. Other investigations for possible etiology of liver disease all came out negative including hepatitis markers, immunoglobulins, autoantibodies, alpha-1 antitrypsin (1.51 g/L-normal 0.98-1.96 g/L) and ceruloplasmin (0.32 g/L-normal 0.20-0.60 g/L). Liver doppler ultrasound was also normal. A muscular rather than a hepatic problem was suspected. For that reason liver biopsy was not done. More focus on the history, and examination of the muscular system uncovered that the child has baseline easy fatigability which progresses over the day. She had difficulty combing her hair and getting up from the ground. On examination bilateral calf muscles hypertrophy with positive Gower sign. Past medical history was uneventful with normal foetal movements and uncomplicated labour at 40 weeks of gestation. The girl's development was also uncomplicated; milestones were reached at the appropriate age, and family history was unremarkable. Muscle enzymes were studied and CPK levels were found to be highly elevated with serial CPK concentrations of 6651, 15831 U/L. Electromyogram and Motor Nerve Conduction were done and reported to be suggestive of congenital myopathy. Her brother and sister were screened with CPK which came out normal. Muscle biopsy revealed some single atrophy as well as myopathic changes such as degeneration and regeneration of muscle fibers suggesting an early stage of muscular dystrophy. Immunohistochemical analyses were compatible with Sacroglycanopathy, possibly Limb Girdle Muscle Disease Type 2C (LGMD, 2C), which was further confirmed by molecular genetic testing. The patient was referred to the Pediatric Neurology Department. The time interval between the child's presentation to the Pediatric Hepatology and Gastroenterology Clinic and the diagnosis was nearly two months, although almost one year had passed from the initial coincidental finding of elevated AST and ALT until the final diagnosis.

Discussion

Persistently unexplained elevation of ATs is most commonly observed at the present time. A clear elevation of more than ten times the normal range is a well-validated index of cytolysis liver, but a more moderate rise can also reveal a metabolic muscle disease whose diagnosis is sometimes difficult to establish (1,2). ATs are two cytosolic enzymes: ALT essentially has hepatic origin, and secondarily, muscle and kidney (3) origin. AST has a much wider distribution within the liver, but also in the heart, skeletal muscle, kidney and brain. Their physiological levels in plasma are between 5 and 50 IU/L but they depend on the technical laboratory, population reference and the selected distribution range (4). In line with other reports, the increased transaminases in our case also resulted in referral to the Hepatology and Gastroenterology Department for examination and evaluation; and muscle disease did not cross the mind of the assessing physician (5,6). The findings in our patient demonstrate that elevated serum AST and ALT in the absence of signs and symptoms of liver disease should lead to the consideration of occult muscle disease as a probable source. This assumption should be considered only after having eliminated any liver disease and carrying out a thorough interview and a complete physical examination with some laboratory tests. That is why in our case a more focused history and examination of muscular system was carried out, revealing that the child had easy fatigability, which progressed over the day with difficulty combing her hair and getting up from the ground. Calf muscles were hypertrophied with positive Gower sign and high CPK suggesting muscle dystrophy. This was further confirmed by muscle biopsy and molecular genetic testing. Actually, elevated serum ATs may not only indicate hepatic disease but could also stem from muscle or other cellular damage (7). Both CPK level and the ratio between AST and ALT may be of help in differentiating between muscle and liver cell damage (8). The findings in our patient indicate that elevated AST and ALT in the absence of signs of liver disease should lead to the consideration of occult muscle disease. So, the measurement of serum CPK and a careful physical examination are the most useful and cost effective means to correctly identify these patients before carrying out invasive tests such as liver biopsy. This phenomenon has been described in many case reports (4,8) and in a series of five male Taiwanese patients with raised serum ALT and AST in whom signs and symptoms of hepatic disease were absent but evidence of neuromuscular dysfunction was detectable on clinical examination. The ages of these children were between 4 months and 5.5 years. None of the neurological findings were remarkable. The initial ALT and AST values were 114-581 U/L and 183-700 IU/L, respectively. Serum CPK was checked first after 0 to 30 months follow-up and found to be markedly elevated (range, 10.557 IU/L to 62.508 IU/L). Muscle biopsies in all of the five cases showed degenerating and regenerating myofibers with interstitial fibrosis, and genetic studies showed deletions in the *DMD* gene (9). The question thus remains, "What is wise in cases where no or only mild symptoms of the myopathic disease are present?" Thinking of alternative sources of alanine and aspartate ATs can help in avoiding such clinical pitfalls and spare families the anxiety and trauma of unnecessary investigations and delays in diagnosis, which may have prognostic implications. We recommend that when there are no clear clinical findings of hepatic or muscle disease in a child with persistently elevated AST and ALT, a CPK estimation on serum would be a wise step before going to invasive and expensive hepatic investigations including liver biopsy. This case report emphasizes that increased ATs do not always suggest liver disease. Occult muscle diseases should be taken into account in patients with unexplained long-lasting hypertransaminasemia, and therefore the measurement of serum CPK activity and muscle biopsy should be done early for a more correct diagnosis to avoid invasive and expensive investigations such as liver biopsy.

Ethics

Informed Consent: Written informed consent was obtained from the parents for contribution of their child in the current case report and for publication.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.M.K., H.A.A., A.O.A., A.H., Concept: N.M.K., Design: N.M.K., Data Collection or Processing: M.R., K.A., Analysis or Interpretation: M.R., K.A., Literature Search: N.M.K., M.H.H.E.S., A.E.E., H.M., L.M.S., Writing: N.M.K., M.H.H.E.S., A.E.E., H.M., L.M.S.,

Conflict of Interest: No conflict of interest was declared by the authors.

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