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Original Article

Control of Coagulation Abnormalities with Sodium Benzoate in Patients with Argininemia

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ABSTRACT

Aim: This study aimed to evaluate coagulation disorders in patients with argininemia associated with *arginase* 1 gene mutations and the control of these disorders with sodium benzoate treatment.

Materials and Methods: Five argininemia patients followed up in the Pediatric Metabolism Clinic in University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, were included in this study. The patients initially received protein-restricted diet treatment, while their ammonia, platelet count, liver enzymes and coagulation parameters were measured regularly. Later, sodium benzoate was added to the treatment and the same parameters were measured at 1-month intervals.

Results: In the coagulation parameters measured after sodium benzoate treatment, one out of the five patients showed complete improvement, three had partial improvement, and one had no change. In the patients with coagulation disorders, factor VII and IX levels were low, while arginine levels remained above 250 µmol/L.

Conclusion: The pathophysiology of coagulation disorders in patients with argininemia has not yet been fully elucidated, but it is thought that high arginine levels may affect the synthesis of short-lived coagulation factors. Adding sodium benzoate to dietary therapy may contribute to both the control of arginine levels and an improvement in coagulation parameters. This study demonstrates the importance of coagulation monitoring in those patients with argininemia and the potential therapeutic role of sodium benzoate.

Keywords: Argininemia, coagulation disturbance, factor deficiency, sodium benzoate

Introduction

Argininemia [arginase 1 deficiency (ARG1-D), or hyperargininemia; Online Mendelian Inheritance in Man 207800] is an autosomal recessive inherited disease caused by the deficiency of arginase 1, which is a rare type of urea cycle disorder (UCD) (1). It is caused by mutations in the *ARG1* gene located on chromosome 6q23 (2). The UCD consortium study from Europe and the USA reported that the incidence of ARG1 deficiency was estimated to be approximately 1 per 950,000 births (3), accounting for 3.5% of all UCD patients (4). Unlike other UCDs, clinical presentations are complicated and lack specificity, including progressive spastic paraplegia, hyperactivity of deep tendon reflexes, intellectual developmental disability, failure to thrive, seizures, microcephaly and ataxia in late infancy or the pre-school age (5-6). Additionally, neonatal hyperammonaemia and encephalopathy are not common

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features of this disorder. Liver damage ranges from a mild elevation of transaminases to liver failure (7). In addition, coagulation dysfunction is characteristic of argininemia, which is not accompanied by life-threatening haemorrhagic complications, and its mechanism is still unclear (8).

Coagulation disturbances have been reported in ARG1-D patients (8,9). Coagulation dysfunction is characteristic of argininemia without life-threatening haemorrhagic complications, and low levels of factor (F) VII and FIX have been demonstrated, although this mechanism is still unclear (8). Most of the coagulation factors are proteins with a serine protease structure. The activity of serine proteases is controlled by plasmatic serine protease inhibitors (10). Serine protease recognizes a specific region (P1-P10) in the serpin molecule. Most often, arginine is the amino acid at position P1. This interaction can be competitively inhibited by the arginine functional group, free arginine or free guanidine (11). L-arginine (or guanidine) has been shown to inhibit the activation of haemostasis (12).

Previous studies have not reported an effective drug treatment for coagulation disturbances in patients with argininemia. The effectiveness of vitamin K therapy has not been demonstrated in these patients (8,13). In our study, we examined coagulation dysfunction in our patients with argininemia and the effects of sodium benzoate on coagulation dysfunction in addition to the traditional treatment of dietary therapy.

Materials and Methods

Five argininemia patients followed up by Pediatric Metabolism Clinic in University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, whose diagnoses were confirmed by *ARG1* gene sequence analysis, were determined as the study group. This study was approved by the Ethics Committee of the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital (approval no.: 2022.01.35, date: 26.01.2022). Informed consent was obtained from the legal guardians of all participants prior to their inclusion in this study. Procedures were carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Ammonia levels, platelet counts, liver function tests, and coagulation parameters [prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), clotting factor levels] were taken from the patients while they were on a protein-restricted diet only. After sodium benzoate was added to their treatment, the same laboratory tests were repeated at 1-month intervals. Parameters measured before and after sodium benzoate treatment were compared.

Statistical Analysis

Due to the small sample size in this study, formal statistical analyses were not conducted. Instead, the data are presented using descriptive statistics, expressed as mean ± standard deviation (SD).

Results

The summary of the clinical features of the patients is presented in Table I. Cases 1 and 2 and Cases 3 and 4 were siblings. There was consanguinity between the parents. Cases 1 and 2 were of Syrian origin and the family could communicate in Turkish.

The first case was diagnosed late at the 14 years. The patient had severe spastic paraplegia and mental-motor retardation. Height and weight percentiles were quite low (<-2 SD score). She could not walk or speak. Since her oral feeding was inadequate, orogastric tube feeding treatment was applied. At the time of diagnosis, liver transaminases, arginine levels and coagulation parameters were found to be high. With the diagnosis of liver failure, the patient was treated with fresh frozen plasma, N-acetylcysteine and high-dose vitamin K. Although the transaminase values improved with low-protein diet treatment, the coagulation parameters continued to be impaired. However, after the patient was started on sodium benzoate treatment, the INR value returned to normal levels (Figure 1, Table II).

The second case was the sibling of the first case and was diagnosed at the age of 1 through family screening. No clinical findings were detected at the time of diagnosis. A low-protein diet was started. However, the patient could not comply with the diet treatment. During the follow-up, deterioration in transaminase and coagulation parameters was observed. Sodium benzoate was added

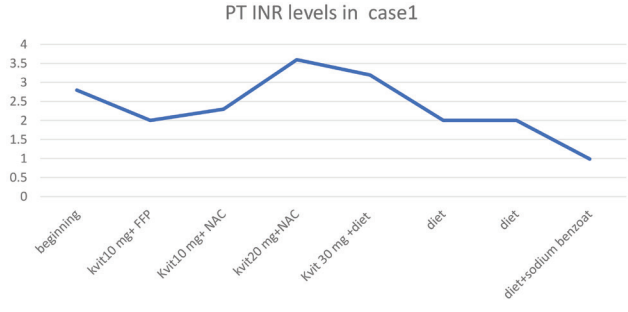

Figure 1. PT INR levels in case 1

PT: Prothrombin time, INR: International normalized ratio, FFP: Fresh frozen plasma

Table I. Clinical characteristics of five patients with arginemia

	Gender (years)	Age at presentation	Current ages (years)	Consanguinity	Coagulation dysfunction	Bleeding sign	Variant of ARG1/ inheritance	Physical examination
Case 1	14	5 years	14	Yes	Yes	No	c.58-3C>G homozygous	Spastic paraplegia; intellectual developmental disability
Case 2	3	1 years	3	Yes	Yes	No	c.58-3C>G homozygous	Hyperreflexia borderline intellectual developmental disability;
Case 3	6	1 years	6	Yes	Yes	No	c.306C>G (p.Ser102ARG) homozygous	Hyperreflexia borderline intelligence
Case 4	2	Neonatal	2	Yes	No	No	c.306C>G (p.Ser102ARG) homozygous	Hyperreflexia language decite
Case 5	6	3 years	6	Yes	Yes	No	c.130+1G>A homozygous	Hyperreflexia borderline intelligence language decite

ARG1: Arginase 1

Table II. Laboratory data before and after sodium benzoate treatment

Variables	**Ref**	**Case 1**		**Case 2**		**Case 3**		**Case 4**		**Case 5**	
Sodium benzoate		**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
PT (s)	8.4-10.6	**11.2**	8.8	**11.5**	**11.9**	**12**	**11.2**	8.7	8.452	**13.5**	**12.99**
aPTT (s)	23.9-33.2	**35.5**	24.5	**39**	**38.2**	**37.9**	**36.1**	30	28.8	**41**	**38.36**
INR	0.8-1.2	**2.5**	0.996	**1.40**	**1.41**	**1.42**	**1.38**	0.92	0.98	**2.2**	**1.46**
FVII, %	50-150	**22**	86.2	**26**	**32**	**38**	**40**	100	100	**25.88**	**28**
FIX, %	50-150	**23.2**	90	**25.8**	**30**	**35.4**	**35**	78.6	82	**20.1**	**25**
AST (IU/L)	0-52	43	32.6	**81**	**78.2**	**55**	**57.6**	41	39.4	**157**	**161.8**
ALT (IU/L)	0-29	38	25.6	**55.4**	**52.8**	**48**	**50.6**	23	17.6	**75**	**72.6**
Albumin (gr/L)	34-54	31.5	32.5	36	40.6	40	38.4	35	37.8	39	44.6
T. bilirubin (µm/L)	0.3-1	0.11	0.15	0.20	0.25	0,27	0.35	0.20	0.15	0.10	0.36
Arginine (µm/L)	18-110	**220**	**195**	**371.6**	**368.5**	**309.8**	**313.2**	**236.6**	**245.3**	**309.3**	**289.3**
Ammoniac (µm/L)	11-51	50	46.4	31	36.31	29	23.5	38	46.4	30	33.7
Effect		Complete improvement		Partial improvement		Partial improvement		No abnormality		Partial improvement	

The distribution of laboratory parameters before and after sodium benzoate treatment is presented in Table II. Sodium benzoate treatment resulted in complete improvement in coagulation parameters (PT, aPTT, INR) in Case 1, and partial improvement in Cases 2, 3, and 5. No abnormal coagulation findings were observed in Case 4. Factor VII and IX levels were low before treatment in Cases 1, 2, 3, and 5, with a post-treatment increase noted, although levels did not fully normalize. Arginine levels remained elevated in cases with coagulation disorders. No significant changes were observed in other liver function tests (AST, ALT, albumin, bilirubin) or in ammonia levels.

PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, F: Factor, AST: Aspartete aminotransferase, ALT: Alanine aminotransferase, T.bilirubin: Total bilirubin

to the treatment without making any changes to the diet treatment he received. A partial improvement in the INR value was observed after one month (Table II).

The third case was diagnosed at the age of 1. Liver transaminases and coagulation parameters, which were normal at the time of diagnosis, began to deteriorate in the sixth year. However, partial improvement in coagulation parameters was observed with the addition of sodium benzoate (Table II).

The fourth case was diagnosed in the neonatal period. Liver transaminases and coagulation parameters remained

normal from the time of diagnosis and throughout the study. Sodium benzoate was administered as part of the study. INR values were evaluated as normal before and after sodium benzoate.

The fifth case was diagnosed at the age of 3 years. At the time of diagnosis, liver transaminases and coagulation parameters were high and were evaluated as liver failure. Despite vitamin K, frozen plasma and low protein diet treatment, the PT INR value remained constant at 2. After the patient was started on sodium benzoate treatment within the scope of the study, a near-normal improvement in the INR value was observed (Table II).

In our study, FVII and IX levels were found to be low in the first, second, third and fifth cases, while other factor levels were normal (Table II).

Arginine levels were below 250 µmol/L in our patients without coagulation disorders. However, arginine levels in 3 patients with coagulation disorders remained above 250 µmol/L despite conventional treatment. Hyperammonemia was not observed in any of our patients with coagulation disorders. No significant change was observed in albumin and total bilirubin values in any patient. Platelet counts were normal. No major or minor bleeding findings were observed in patients with coagulation disorders.

Discussion

While the clinical presentation of ARG1-D varies by individual, most patients appear to have normal development from birth to toddlerhood, with symptoms beginning sometime between the ages of 1-3 years (14). Coagulation dysfunction is also a characteristic of argininemia, however, this symptom is not accompanied with life-threatening haemorrhagic complications and the underlying mechanisms remain unclear (8).

Liver disease in UCDs likely results from chronic accumulation of amino acids such as glutamine, toxic products such as argininosuccinate and guanidino compounds, ongoing steatosis and glycogen deposition, a deficiency of essential amino acids and nitric oxide, and a failure of adequate adenosine triphosphate production consequent to mitochondrial dysfunction (15,16).

The liver is the most important organ where all coagulation factors are synthesized. In chronic liver diseases (CLD), almost all coagulation factors and inhibitors are reduced. In acute liver failure (ALF), FV and FVII, which have short half-lives, decrease first, followed by FII and FX. FIX and FXI levels are normal in ALF and low in CLD (16).

In our study, we found low levels of factors VII and IX in our patients with impaired coagulation. Other factors were normal. There were no signs in our patients of minor or major bleeding, which are symptoms of clotting factor deficiency. In a recent study similar to our study, FVII and FIX levels were found to be low, while other factors related to vitamin K, such as factors II and X, were found to be normal. Contrary to our study, petechiae and ecchymosis, which are signs of minor bleeding, were observed in some of the patients in another study. In that same study, no hyperammonemia was observed in any of the patients, which is similar to our study (8). Laemmle et al.'s (17) study demonstrated increased PT INR unresponsive to vitamin K during elevated ammonia measurements in ornithine transcarbamylas cases with ALF. They suggested that hyperammonemia may affect the synthesis of short-lived clotting factors (17).

The main goal of long-term management for ARG1-D patients is to lower the levels of plasma arginine. The current standard of care is dietary restriction, aimed at limiting arginine and protein intake through a low-protein diet, often supplemented by essential amino acids (1,14). Although dietary modifications can produce modest reductions in plasma arginine, levels remain markedly elevated in most patients, as arginine flux is largely due to whole body protein turnover and minimally affected by dietary intake (15). In our 3 patients with impaired coagulation, their blood arginine levels remained above 250 µmol/L throughout the study. There was a moderate elevation in liver transaminase values. In one of our patients whose coagulation parameters improved, the plasma arginine level remained below 200 µmol/L. In a study by Cui et al. (9), the range of blood arginine concentrations was 187-810 µmol/L, with an average of 459±209 µmol/L. While liver transaminases were elevated in nine patients, no significant changes were observed in albumin and total bilirubin, and platelet counts were normal. Results from coagulation analysis showed that PT was prolonged, PT INR increased in nine patients, and aPTT was significantly prolonged (>10 s) in five patients (9).

Sodium benzoate is a widely used food and drink preservative and is also an established and accepted adjunctive treatment in the European guidelines for UCDs and all causes of hyperammonemia (14,18). Nitrogen scavenger drugs such as sodium benzoate, sodium phenylacetate and glycerol phenylbutyrate may also be used to reduce the risk of hyperammonemia by removing excess nitrogen through an alternative pathway but have no effect on arginine levels

(15). Levels of guanidino compounds are increased even when arginine is minimally increased or normal. Therefore, dietary arginine restriction does not appear to be sufficient for metabolic control. Sodium benzoate can bind to glycine and reduce the substrate concentration (19). In our study, we thought that in addition to reducing arginine levels with diet, applying sodium benzoate as a glycine scavenger could reduce guanidinoacetate compounds and have a positive effect on coagulation in addition to its nitrogen scavenger effect. We observed that coagulation parameters were completely improved in one of our patients with the addition of sodium benzoate treatment, and that coagulation disorders were limited in our other patients.

Liver transplantation effectively treats ARG1-D in the liver, normalizing arginine and ammonia levels and stopping neurological deterioration, making strict protein restriction and nitrogen scavengers unnecessary (20). It constitutes the ultimate treatment option for patients with recurrent attacks of hyperammonemia (9). However, it is a high-risk operation, especially for those with ALF or encephalopathy. Enzyme replacement therapy is another treatment option which is currently under investigation, involving intravenous injections of pegylated human recombinant arginase 1 (pegzilarginase) (21).

Study Limitations

This study has several limitations. Firstly, the small sample size limits the generalizability of the findings and reduces the statistical power to detect significant differences. Due to the rarity of ARG1 deficiency, recruiting a larger cohort was challenging. Additionally, dietary compliance varied among the participants, which may have influenced the biochemical and clinical outcomes. Finally, some laboratory parameters, such as guanidino compounds and nitric oxide metabolites, were not measured, limiting insight into the underlying pathophysiological mechanisms. Future studies with larger sample sizes and longer follow-up periods are warranted to better understand coagulation disorders in ARG1 deficiency and the therapeutic role of sodium benzoate.

Conclusion

In conclusion, it should be emphasised that ARG1-D patients have coagulation disorders in addition to their known clinical findings. Coagulation tests and factor levels should be included among the follow-up parameters of ARG1-D patients. No effective treatment has been reported for the treatment of coagulation disorders in these patients. Although it has been reported that peak plasma arginine levels may be effective in the development of coagulation abnormalities, further research is needed on its underlying mechanisms and treatments. We report that sodium benzoate treatment can be used in addition to diet therapy in the control of coagulation parameters in ARG1-D patients, even if ammonia levels are not high.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital (approval no.: 35, dated; 26.01.2022).

Informed Consent: Informed consent was obtained from the legal guardians of all participants prior to their inclusion in the study.

Footnotes

Authorship Contributions

Concept: N.Ü.E., Design: N.Ü.E., H.Ö., Data Collection or Processing: N.Ü.E., A.G., Analysis or Interpretation: N.Ü.E., Literature Search: N.Ü.E., Writing: N.Ü.E.

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