Characteristics of Argininemia and Effect of Liver Transplantation-the Largest Experience in China

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Abstract

Background: Argininemia is a rare urea cycle disorder due to arginase-1 deficiency, characterized by progressive spastic paraplegia. Coagulation dysfunction has been reported in few researches, and the pathophysiology is still unclear. Advances in diagnosis and treatment have increased the number of patients receiving effective management; however, not all symptoms are prevented under traditional treatments, and there is no consensus on liver transplantation (LT) for the treatment of patients with argininemia.

Methods: We conducted a retrospective study of patients who had been done LT in our center between January 2015 and November 2019. Eleven patients with argininemia were included for their poor response to protein restriction dietary and alternative therapy of nitrogen scavengers. The details on coagulation, liver function, histopathological and morphological examination of liver samples, and other clinical presentations were extracted. The Grading Scale for evaluating neurological status and classification of physical growth and quality of life was used to assess the effect of LT.

Results: All patients demonstrated hyperarginine, progressive neurological impairments, among whom nine patients presented coagulation dysfunction pre-oparation. After LT, the coagulation index and plasma arginine returned to normal in all patients, and neurological symptoms, growth deficit, and quality of life improved significantly without any severe complications. All patients survive to date.

Conclusions: Our findings indicated that coagulation abnormality was a typical presentation of argininemia. LT can prevent progressive neurological impairment and restore metabolic disorders entirely.

Background

Argininemia (arginase deficiency or hyperargininemia; OMIM 207800) is an autosomal recessive inherited disease caused by a deficiency of arginase-1 (ARG1)[1]. Inborn mutations cause this genetic disorder in the gene *ARG1*, located on chromosome 6q23.2, resulting in partial or complete loss of enzyme function. 70 + mutations have been found fairly relatively spread throughout the gene *ARG1*[2]. The disease is pan-ethnic, with an estimated 1 in 2 million live births[1, 3, 4]. The accumulation of arginine in blood and other fluids is the hallmark of argininemia and presents in all patients.

Compared with other urea cycle disorders (UCDs), clinical presentations are complicated and lack specificity, including progressive spastic paraplegia, seizures, growth deficit, intellectual developmental disability, microcephaly, irritability, lethargy, nausea, reduced appetite, and ataxia, while hyperammonemic encephalopathy is rarely observed in argininemia[3, 4]. Besides neurological damage, liver damage ranges from a mild elevation of transaminases to liver failure[5]. Additionally, coagulation dysfunction is the characteristic of argininemia, which is not accompanied by life-threatening hemorrhagic complications, and the mechanism is still unclear[6]. Studies have suggested that elevated plasma ammonia is an important cause of clotting disorders in UCDs[7]; however, there is no consensus on whether coagulopathy in patients with argininemia is related to elevated plasma ammonia.

Treatment should be started with the combination of protein restriction dietary, supplementation of essential amino acids, sodium benzoate, and sodium phenylbutyrate. However, neurological symptoms and coagulation disorder could not be entirely prevented by conventional treatments[6], which may successfully reduce or even normalize plasma arginine levels, but the catabolites of arginine can remain elevated, and some of these guanidino compounds are neurotoxic[8]. Although LT was suggested to cases with hepatic fibrosis and cirrhosis, plasma levels of arginine and its metabolites were normalized by LT, which can significantly alleviate symptoms[8], and the function of LT for argininemia were rarely reported.

Due to there were few studies on LT for patients with argininemia, any detailed description of the individualized treatment plan and clinical presentations may provide important information and unique insights, helping to interpret the underlying physiopathologic mechanism and propose a timely intervention LT for such cases. All patients in the present study had been treated with LT in our center; we describe the characteristics of eleven patients with argininemia and evaluate the effect of LT-the largest experience in China.

Methods

Data Collection

A retrospective analysis of eleven patients (seven female, four male) with argininemia admitted to Liver Transplantation Center of Beijing Friendship Hospital, Capital Medical University, between January 2015 and November 2019. Blood arginine levels were analyzed by liquid chromatography tandem mass spectrometry method, and gene sequencing was performed in all patients to confirm mutations in the *ARG1* gene. The indications for LT were progressive neurological impairment and metabolism decompensation with traditional treatment. The transplantation score was assessed according to previous report[9], and the scoring system was listed in Supplementary table 1. All patients had undergone LT, and the operations were approved by the Ethics Committee of Beijing Friendship Hospital. According to report[10] of Morioka et al., the neurological status, physical growth, and quality of life were evaluated, and the grading scale was listed in Supplementary table 2. This retrospective study was conducted in accordance with the Declaration of Helsinki, and no organs from executed prisoners were used for LT.

Retrospective analysis of blood ammonia level, platelet count, aminotransferase, total bilirubin, albumin, prothrombin time (PT), international normalized ratio (INR), activated partial thrombin activity time (APTT), plasma arginine concentration, and other laboratory indictors. Data such as neurological manifestations, age at onset/operation, gender, gene mutations, and heights were collected to explore the clinical characteristics of these patients. And the patients were followed up in the clinic and by telephone.

Statistical analysis

SPSS version 22.0 was used for statistical analysis. Data were represented as mean(M) ± standard deviation(SD). Correlation studies between plasma ammonia levels, INR values, and APTT were performed by calculating Pearson's correlation coefficient with the two-tailed test, and $p<0.05$ was considered significant.

Results

Preoperative clinical characteristics

Genetic analysis revealed two allele mutations in the *ARG1* gene of all patients, which derived from their parents, respectively, consistent with autosomal recessive inheritance characteristics. Among the eleven patients, sixteen mutations were identified, and seven mutations, c.23T > C in exon1, c.51delG in exon1, c.246_248delAAA in exon3, c.603delT in exon6, c.756-757insACAT in exon7, c.826 + 2T > C in exon7, and c.922C > T in exon8 were novel. Three patients were found by neonatal screening(Case 3, 4, and 6), and confirmed by gene sequencing. And the other eight were diagnosed by plasma amino acid analysis and gene sequencing after symptoms developed. The eleven patients' average onset age was 23.7 ± 29.1 months old (range, 4-108 months). The preoperative patient main characteristics of patients were shown in Table 1.

Table 1
Clinical characteristics of eleven patients with argininemia

	Gender	Age at presentation (months)	Current ages (months)	Age at operation (months)	Gene Mutations	Mutation at Protein Level	Neurological presentations	Procedure
Case1	Female	9	96	33	c.32T > C(exon1) c.232dupG(exon3)	p.I11T p.S77fs	Spastic paraplegia; Intellectual developmental disability; Language deficits	DDLT
Case2	Female	12	82	24	c.603delT(exon6) c.756–757insACAT(exon7)	p.T201fs p.L252fs	Spastic paraplegia; Seizure; Intellectual developmental disability; Language deficits	DDLT
Case3	Male	4	47	12	c.603delT(exon6) c.703G > A(exon7)	p.E202kfs*5 p.G235R	Epileptic seizure; Intellectual developmental disability; Language deficits	DDLT
Case4	Male	18	40	24	c.263–266delAGAA(exon3) c.374C□T(exon4)	p.Lys88fs p.A125V	Spastic paraplegia; Intellectual developmental disability; Language deficits; Ataxic tremor of the upper limbs	LDLT
Case5	Female	22	56	42	c.703G > A(exon7) c.295G > A(exon3)	p.G235R p.G88R	Spastic paraplegia; Intellectual developmental disability; Language deficits	LDLT
Case6	Female	8	23	14	c.262–265delAAGA(exon3) c.23T > C(exon1)	p.K88Rfs*44 p.I8T	Epileptic seizure; Intellectual developmental disability; Language deficits	LDLT
Case7	Male	108	174	166	c.263–266delAGAA(exon3) c.647T > C(exon8)	p.K88Rfs*45 p.L216P	Spastic paraplegia; Language deficits	LDLT
Case8	Female	6	65	62	c.53G > A(exon1) c.703G > A(exon7)	p.G18E p.G235R	Spastic paraplegia; Intellectual developmental disability; Language deficits	LDLT
Case9	Female	24	75	70	c.51delG(exon1) c.826 + 2T > C (exon7)	p.K17fs Unclear	Epileptic seizure; Spastic paraplegia; Intellectual developmental disability; Language deficits; Ataxic tremor of the upper limbs	LDLT
Case10	Male	30	57	52	c.32T > C (exon1) c.246_248delAAA (exon3)	p.I11T p.K83del	Epileptic seizure; Spastic paraplegia; Intellectual developmental disability; Language deficits	LDLT
Case11	Female	20	34	32	c.263–266delAGAA (exon3) c.922C > T (exon8)	p.K88Rfs*45 p.R308W	Spastic paraplegia; Intellectual developmental disability; Language deficits	DDLT

DDLT: deceased donor liver transplantation; LDLT: living donor liver transplantation.

Nine patients presented with typical progressive spastic paraplegia of the lower extremities, and two patients (Case 4 and 9) manifested ataxic tremors of the upper extremities. Physical examination showed hypermyotonia, muscle weakness of bilateral lower limbs, hyperreflexia of knee and ankle reflex, positive ankle clonus, and Babinski signs. Two patients (Cases 3 and 6) did not show obvious dyskinesia, maybe due to their younger age. Four patients (cases 3, 6, 9, 10) had generalized tonic-clonic seizures as the initial symptom, and the electroencephalogram showed continuous generalized spikes or polyspike/spike-slow complex wave discharge (Fig. 1). Topiramate and levetiracetam were used to control seizures. Five patients (Cases 1, 8, 9, 10, and 11) could not walk independently without help during the preoperative evaluation. Cases 8 and 9 were initially misdiagnosed with CP and received rehabilitation training, but the symptoms deteriorated. Only Case 7 showed slow speech, and the rest lost the ability to speak sentences and showed intellectual developmental disability. Growth deficits were observed in seven patients. All patients manifested emotional instability and irritability. Hyperammonemia encephalopathy was not seen in this series of patients. The data for evaluating neurological status and classification of physical growth and quality of life were listed in Table 3.

Laboratory data and liver imaging before LT

The maximum blood arginine concentration was 187–810μmol/L, with an average of 459 ± 209μmol/L. All patients had elevated liver transaminases, while albumin and total bilirubin showed no significant changes, and platelet count was normal. The coagulation analysis indicated that PT was prolonged and INR was increased in nine patients, and APTT was significantly prolonged in five (> 10s) patients. Clotting factors assay was not a routine check of the preoperative evaluation, so patients in this group did not further assess coagulation factor deficiency. At the same time, hyperammonemia was found in the same blood sample of ten patients. The data were listed in Table 2. There was a positive Pearson correlation between APTT and INR, but there was no significant correlation between them and plasma ammonia. None of the patients presented with significant bleeding symptoms. Abdominal computed tomography showed mild hepatomegaly in two patients (Cases 2 and 9). An ultrasound examination in four patients (Cases 3, 6, 8, and 9) showed enhancement of liver echogenicity.

Table 2
Laboratory data of eleven patients in this group

	Case1	Case2	Case3	Case4	Case5	Case6	Case7	Case8	Case9	Case10	Case11	Reference range
Ammonia (μmol/L)	157	67	126	55	56	52	57	49	67	37	61	0–45
PT(s)	26.4	18.3	36.4	24.7	14.5	51	16.5	26.5	15	11.7	12.2	9.6–13.5
INR	2.68	1.58	3.14	2.19	1.27	4.6	1.51	2.39	1.38	1.08	1.13	0.8–1.2
APTT(s)	53.7	57.7	63.8	39.4	27.6	83.9	34.2	53.9	34.1	34.2	32.9	21–34
Platelet(*10^9/L)	283	333	200	384	350	339	201	350	173	271	200	100–300
AST (IU/L)	58	64	120	214	136	173	39	87	78	21	99	0–40
ALT (IU/L)	48	78	210	195	277	227	39	142	158	35.5	58.7	0–40
Albumin(g/L)	38.6	41.1	37	32.7	31.1	32.4	38.1	43.6	34.3	39.7	36.5	40–55
Total Bilirubin(μmol/L)	6	4.47	5.61	17.52	7.22	6.65	13.36	12.67	9.49	9.33	7.76	3.42–17.1
Blood arginine concentration# (μmol/L)	349.8	810	732.4	716.3	488.7	459.9	289.1	353.8	420	245	187.05	5–25

PT: Prothrombin Time; INR: International Normalized Ratio; APTT: Activated Partial Thromboplastin Time; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; #,maximum concentration of blood arginine.

Table 3
The data of neurological status and classification of physical growth and quality of life and transplantation score

	Neurological status Pre-and/ Post LT	Physical growth* Pre-and/ Post LT	Quality of life Pre-and/ Post LT	Transplantation score
Case1	4/3	Delayed/Slightly delayed	Poor/Poor	13
Case2	3/0	Slightly delayed/Normal	Poor/Excellent	12
Case3	3/1	Delayed/Normal	Poor/Fair	11
Case4	4/2	Normal/Normal	Poor/Fair	10
Case5	3/2	Slightly delayed/Normal	Poor/Fair	12
Case6	2/0	Normal/Normal	Fair/Good	9
Case7	2/1	Normal/Normal	Fair/Fair	10
Case8	3/2	Delayed/Slightly delayed	Poor/Fair	12
Case9	3/2	Delayed/ Delayed	Poor/Fair	13
Case10	3/2	Delayed/Delayed	Poor/Fair	10
Case11	3/2	Normal/Normal	Poor/Fair	9

*Physical growth was evaluated by comparing the height of each patient with those in the standard growth curve, and was expressed as a multiple of the standard deviation (SD) of the deviation from the standard curve.

The consequences after LT and operative procedures

All patients seek LT because their symptoms gradually deteriorated after conventional treatment. The mean transplantation score was 11.0 ± 1.5, which an absolute indication for LT[9]. Of these eleven patients, seven received living donor liver transplantation (LDLT), the other four received deceased donor liver transplantation (DDLT). All patients underwent LT by a standard procedure[11, 12]. The average age at LT was 48.3 ± 43.3 months old. The mean value of graft-to-recipient weight ratio (GRWR) was 2.5% (1.3%-3.8%). Of the group of LDLT, the donors were heterozygote. Immunosuppressive treatment consisted of tacrolimus, mycophenolate mofetil, and low-dose corticosteroids. And postoperative complications, including biliary stricture affected case 1 and portal vein stenosis affected case 3, no major complications in other patients. The postoperative follow-up period ranged from 2 to 63 months. To date, the overall patient and graft survival rate was 100% and 100%, respectively.

All patients were emotionally stable, and their irritable state completely disappeared after LT. Diet returned to normal without protein aversion. Although not all symptoms alleviated completely, the neurological status improved, and the growth deficit corrected significantly. The knee-jerk reflex of patients affected by spastic paraplegia returned to normal, and the hypermyotonia of the lower extremity improved significantly at rest; however, *gastrocnemii* did not recover entirely. Four patients affected by epilepsy remained seizure freedom without any antiepileptic drugs after LT. The language expression and speech fluency were significantly enhanced. The behavioral and intellectual gap between patients and the average population was gradually narrowing. Plasma ammonia and coagulation dysfunction within one month and plasma arginine within six months returned to normal after the operation. The quality of life improved in the short-term follow-up. The data were listed in Table 3. Of course, 2–3 immunosuppression drugs were used in the last eight patients less than one year after the operation, which affected the quantitative value of life assessment scores.

Histopathological findings in livers

Hematoxylin-eosin (HE) staining showed swollen hepatocytes, lymphocytes infiltration, and large patchy fatty vacuolar in hepatocytes. Such swollen "ballooned" cells contained normal-sized central nuclei (Fig. 2A). The highly swelling hepatocytes with different sizes of lipid droplets can be seen on the electron microscope, and the gap between them enlarged. The number of mitochondria increased, and the ultrastructure was unclear. The endoplasmic reticulum was normal in appearance. A large number of collagen fibers are deposited between hepatocytes and in the Disse space (Fig. 2B).

Discussion

ARG was discovered in mammalian liver tissue in 1904. Two isoenzymes, ARG1 and ARG2, were encoded by different genes in mammals[13, 14]; ARG1 was expressed highest in the liver cell cytosol, while ARG2 was mainly expressed in the prostate and kidneys. ARG1 was the final enzyme of the urea cycle, converting arginine to urea and ornithine[14]. And the deficiency of ARG1 could lead to impaired ureagenesis, which characterized by hyperargininemia[3]. The *ARG1* gene was located on chromosome 6 (6q23.2) and comprised eight exons, and mutations in the gene caused

changes in the enzyme structure that prevent it from functioning correctly[15]. Although the functions of the two enzymes are not the same, functional overlap between them may explain why severe hyperammonemia was absent in patients with argininemia[5, 16].

The pathological mechanism of argininemia in neurological damage is still unknown, which may be related to the direct effect of arginine or its metabolites, such as guanidino compounds and nitric oxide(NO)[5]. Previous studies have suggested that guanidino compounds could cause damage to the brain by oxidative stress[17]. Plasma metabolomic data from 13 argininemia patients showed elevated guanidino compounds, guanidinoacetate, argininate, 2-oxoarginine, and N-acetylarginine contributions to the phenotype[18]. The conventional treatment can lower plasma arginine levels and prevent symptoms, but the arginine's catabolites can remain elevated[4, 8]. LT can normalize the arginine level and its metabolites to average ranges, which is not achieved by traditional treatment[8]. In this research, the neurological status and the quality of life improved in most patients, supporting the idea that LT can prevent progressive aggravation of neurological impairment; not all neurological impairments were reversed[8]. According to this study, it appeared that the ankle spasms were challenging to disappear.

In addition, the neurophysiological evaluation data of one patient (not shown) showed that the central motor conduction time was prolonged, while the peripheral motor conduction time, somatosensory evoked potential, electromyography, and nerve conduction velocity were within the normal range, suggesting that corticospinal tract impairment was involved in the pathophysiologic mechanism. The latest research shows that argininemia can cause dysmyelination in brain white matter, indicating that the pathogenesis of argininemia is related to a reduction of oligodendrocytes[19]. Mitochondrial homeostasis was disrupted for the accumlation of arginine in the arginase deficiency model of *Caenorhabditis elegans*. At the same time, the genetic inactivation of the mitochondrial basic amino acid transporter SLC-25A29 could rescue the mitochondrial defects, meaning energy metabolism impairment may damage the nervous system[20]. At the same time, NO induces demyelination by impairing the energy metabolism of oligodendrocytes[21]. Lesion of corticospinal injury caused by oligodendrocyte energy metabolism disorder may be responsible for dyskinesia. Additional studies will be needed to elucidate the pathophysiological mechanism.

A study has found that patients with two severe mutant alleles may indicate of LT because they are less effective at rigorous dietary control[22]. This group of patients had poor responses to dietary therapy. The genetic analysis revealed that they were compound heterozygotes, and the mutations in six patients(Cases 3–8) were considered severe[22]. Compared with homozygotes, animal models showed heterozygotes with mild symptoms[19]; however, many studies have suggested that there is no significant correlation between genotype and phenotype[2]. The data of this study implicated that heterozygotes without clinical symptoms can act as donors for argininemia. Age of onset, duration of arginine effect, peak plasma arginine, the sensitivity of the nervous system to arginine and its metabolites, and genotype may be related to recovery, but the underlying mechanism and correlation need to be further studied[4].

In addition to nervous system damage, the effect on the liver was often manifested as mildly elevated ammonia and transaminase. Although the mechanism of liver injury in UCDs was still unclear, hyperammonemia was considered to be a significant cause of liver damage[6, 7]. Coagulation disorder with hyperammonemia episodes has been described previously, while there is no consensus on their relationship[3, 6]. The histopathological results of this group are consistent with those previously reported[23] and are similar to the trend of hepatocellular edema and reversible changes caused by hyperammonemia[24]. Combined with imaging results and laboratory data, we speculate that liver dysfunction might be caused by hyperammonemia in patients with argininemia[5].

It has been claimed that hyperammonemia can restrict liver protein synthesis, especially for liver-derived proteins with short plasma half-life. Decreased clotting factor Ⅱ levels and increased INR have been observed in patients with ornithine transcarbamylase deficiency (OTCD) during hyperammonemia episodes[7]. In patients affected by acute liver failure, the increased INR was positively correlated with plasma ammonia levels, suggesting it was a sensitive index to reflect liver dysfunction associated with plasma ammonia[7]. However, one case reported no correlation between coagulation dysfunction and plasma ammonia or serum albumin levels, suggesting heterogeneity of etiology of liver damage in patients with OTCD[25]. Clotting factor Ⅱ is considered a sensitive indicator of synthetic liver function, but it was within the normal range in patients with argininemia[6]. According to the report, the deficiency in clotting factors did not result from the hepatic involvement of arginase deficiency[6]. In our study, APTT and INR were positively correlated, indicating a common pathway for coagulopathy. No correlation was found between INR and plasma ammonia; we speculated that coagulopathy was independent of the patient's metabolic status and unrelated to hyperammonemia[6].

PT was prolonged and INR was increased in nine patients. APTT was prolonged > 10 s in five patients with hyperammonemia, which is different from a previous report[6]. The phenomenon may be related to the disease severity of patients in another study. Despite the severe clotting disorder, none of the patients had a life-threatening hemorrhage, suggesting some underlying metabolic abnormalities may be involved in those patients, such as the decrease in clotting and anticlotting factors[7, 26]. Unfortunately, we have not verified the hypothesis.

In conclusion, we suppose that hyperammonemia may cause hepatocyte damage in patients with argininemia. Still, it may be irrelevant to coagulation dysfunction, and other potential mechanisms may play an important role. The coagulation dysfunction in hyperargininemia may be caused by NO, for the cycle of arginine metabolism is disrupted by arginase deficiency, leading to greater production of NO[3–5, 16], which has an anticoagulant effect[27]. The active form of coagulation factor Ⅱ stabilizes blood clotting; however, NO has an inhibitory effect on it by S-nitrosylation of a cysteine residue, resulting in clot solubilization or suppression of clot formation, which may be responsible for the prolonged PT and INR. Also, as the principal substrate for NO synthase, L-arginine suppresses the expression of tissue factors in human microvascular

endothelial cells, which is a critical determinant of thrombin generation[28]. We hypothesized that clotting dysfunction is related to inhibition of tissue factors by high levels of arginine and clot suppression by overproduction of NO in patients with ARG1 deficiency.

In this study, the coagulation abnormalities returned to normal after LT because the arginine cycle can be restored by LT through arginase supplementation. On the other hand, the persistence of clotting dysfunction in other groups supporting the function of NO because metabolites of arginine were not normalized by conventional treatment[5, 6, 8]. In the future, mechanism research on NO will help to explain the phenomenon of patients with argininemia.

Although it was the largest study on LT for argininemia, selection bias may be inevitable as a single-center retrospective study. Due to the rarity of the disease, it is difficult to conduct large cohort studies. Advanced and detailed laboratory analyses, longer follow-up, research on the arginine cycle, and the animal model establishment will help elucidate the exact mechanism of argininemia. In the future, developmental delay, protein tolerance, medication, and neurological status need to be observed in the long run to explore the efficacy of LT in patients with argininemia, and we are doing so.

Conclusion

This study showed coagulopathy is a crucial feature of patients with ARG1 deficiency. Although the exact mechanism needs further research, coagulation functional analysis should be a routine examination in patients with argininemia. LT is an effective treatment for patients with poor response to traditional therapy.

Abbreviations

APTT, activated partial thromboplastin time; ARG, arginase; CP, cerebellar ataxia; DDLT, deceased donor liver transplantation; GRWR, graft-to-recipient weight ratio; INR, international normalized ratio; LDLT, living donor liver transplantation; LT, liver transplantation; NO, nitric oxide; OTCD, ornithine transcarbamylase deficiency; PT, prothrombin time; UCDs, urea cycle disorders

Declarations

Ethics declarations:

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration. This study was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University(2020-P2-094-01). We declare that no organs from executed prisoners were used at Beijing Friendship Hospital, Capital Medical University. All the operations were approved by the Ethical Committee of Beijing Friendship Hospital, Capital Medical University, and all living donors were voluntary and altruistic. Informed consent were obtained from all individual guardians of participants included in the study.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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Availability of data and materials

For further details, the datasets analyzed during the current study are available from the corresponding author on reasonable request. Due to the perioperative data may be updated over time, only one years within the publication date is available.

Authors' contributions

ZJZ, LYS and LW: study concept and design. BC: data collecting; manuscript writing. BC prepared figures and tables. WQ, ZGZ、BC and YL: statistical analysis and analysis of data; ZJZ and LYS study supervision; critical revision of the manuscript for important intellectual content. All

authors read and approved the final manuscript.

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Figures

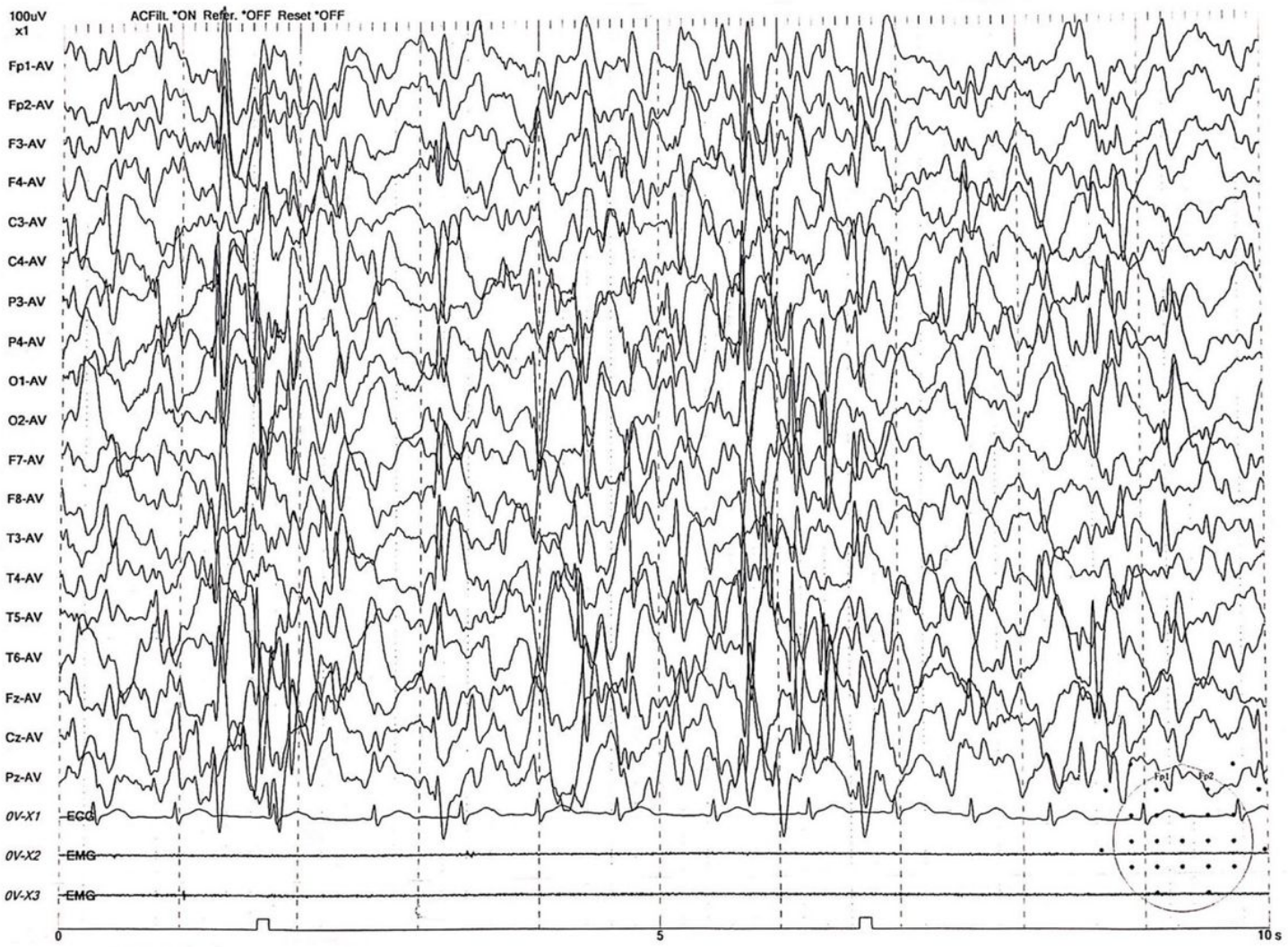

Figure 1

The electroencephalography (EEG) characteristics of a patient with argininemia. Interictal EEG of the case 10 showed bilateral parieto-occipital, central, and mid-posterior temporal regions are dominated by continuous asynchrony medium-high amplitude spikes, polyspike/spike-slow complex wave discharges.

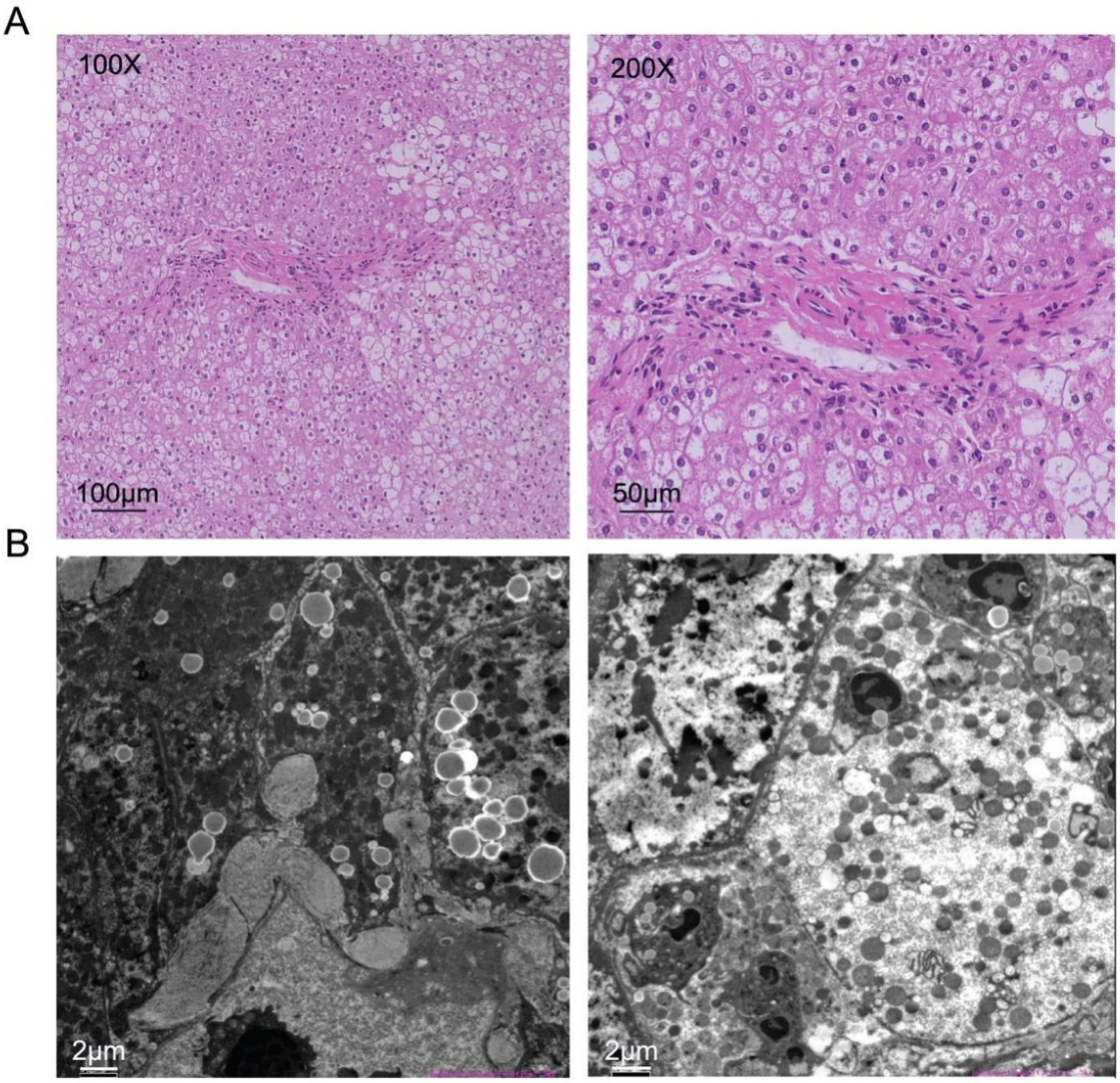

Figure 2

Pathological characteristics of liver in patients with arginemia. A: HE staining of liver showing swollen "ballooned" hepatocytes, patchy fatty vacuolar, lymphocytes infiltration portal areas. B: Electron microscopy found that the damaged hepatocytes were highly swollen, mitochondria with unclear ultrastructure increased, lipid droplets were diffuse, and the shape and disposition of the endoplasmic reticulum were normal.

Supplementary Files

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- Supplementarytable1.docx
- Supplementarytable2.docx