The Main Neurological Dysfunctions in Hyperargininemia—Literature Review

André Eduardo Almeida Franzoi1*, Marcelo Manukian Patti1, Débora Delwing Dal Magro2 and Daniela Delwing de Lima3

1Department of Medicine, University of the Region of Joinville, Joinville, SC, Brazil
2Department of Natural Sciences, Exact and Natural Sciences Center, Regional University of Blumenau, Blumenau, SC, Brazil
3Post Graduation Program in Health and Environment, University of the Region of Joinville, Joinville, SC, Brazil

*Corresponding author: André Eduardo de Almeida Franzoi, Department of Medicine, University of the Region of Joinville, Paulo Malschitzki Street, 10 - Zip Code: 89201-972, Joinville, SC, Brazil, Tel: +55-47-99106-7944, E-mail: andrefranzoi@hotmail.com

Abstract

Objectives: To demonstrate what are the main neurological dysfunctions within the hyperargininemia and other aspects of the disease in order to provide knowledge and an update on the issue.

Methods: We conducted a literature search on reliable databases (PubMed/MEDLINE, Scielo/LILACS and UptoDate) from 1960 to 2018. The selection considered the most relevant articles, including 49 papers and 1 book for this narrative literature review.

Results: Each of the selected materials was studied aiming to the formation of a cohesive and clear article. The main topics were sequenced in: clinical manifestations, diagnosis, genetics, and treatment.

Conclusions: Hyperargininemia is a rare and underdiagnosed disease, but it is benign due to unusual severe hyperammonemia. The main clinical signs are neurological, such as spasticity, ataxia, hyperreflexia, incoordination, paresis, bilateral Babinski sign, tremor and seizures. The initial suspicion occurs with retraction of the Achilles tendon and spasticity. The therapy focuses into reducing plasma levels of arginine and maintain a normal ammonia plasma concentration.

Keywords

Urea cycle, Arginase deficiency, Hyperargininemia, Guanidino compounds, Oxidative stress and its combinations

Introduction

Arginine is an essential amino acid. This compound plays an important role in various body functions including cell division, wound healing, removal of ammonia, immune function, and release of hormones. The arginase 1 is a hepatic enzyme that is the faulty component in urea cycle. The urea cycle is represented in Figure 1 with focusing on arginine. When in normal function, the enzyme catalyzes the reaction of conversion of the arginine in ornithine and urea. However, in hyperargininemia, this enzyme is faulty and the concentrations of arginine in the plasma increases. The gradual accumulation of ammonia in plasma (hyperammonemia) is even more severe to the central nervous system (CNS) [1-3].

This disorder is uncommon when compared with other disorders of the urea cycle. The development of hyperammonemic encephalopathy is not observed in all cases. Other disturbances in the urea cycle can already be identified in the neonatal period or in the beginning of childhood just by the neurological clinical sign appearance. However, in the hyperargininemia, these signs generally do not appear prematurely [4,5].

Quantitative studies point to average prevalence rates of the disorders of the urea cycle more studied in the proportion of 1:8200 births in the United States. Therein, stands out that the hyperargininemia presents incidence rates of 1:2,000,000 live births [3,6-8].

The deficiency of the ornithine transcarbamylase enzyme presents higher rates of prevalence inside the disorders of the urea cycle. Yet the hyperargininemia and the deficiency of N-acetyl glutamic synthase are the less frequent disturbances of the group [3,9].

Citation: Franzoi AEA, Patti MM, Magro DDD, de Lima DD (2018) The Main Neurological Dysfunctions in Hyperargininemia—Literature Review. Int J Neurol Neurother 5:074. doi.org/10.23937/2378-3001/1410074

Accepted: June 23, 2018; Published: June 25, 2018

Copyright: © 2018 Franzoi AEA, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
The main clinical signs are neurological. The illness shows the first symptoms in the childhood period. It is not common the detection of the hyperammonemia and encephalophaties in the newborn. The symptoms usually appear in the first two or four years of life. The progressive spasticity, the regression in the development and the reduction of the mental ability are very common [2].

In rare cases, from 3-months-old to 4-years-old of life, it may have the psychomotor deterioration, which is a sign of hyperammonemia. The hyperammonemia generates the deterioration of clinical symptoms gradually more significant [13].

The epilepsy and the progressive spastic diplegia are not common in newborns and children under 4-years-old. The newborns may present irritability and decrease in the alert state with the introduction of the bovine milk [9, 14].

Cases of sharper hyperammonemia have already been reported, including, the abrupt evolution and fatal outcome. In a newborn patient with high plasmatic concentrations of arginine and glutamine in the liquor, the hyperammonemia got intensified. This dysfunction generated cerebral edema and tachypnea with progression to death [15].

The severe spasticity is a common alteration in the hyperargininemia, possibly presenting relation with the skeletal abnormalities. There are relates of patients with this condition that received treatment with valproic acid. They developed encephalopathy hyperammonemia [16, 17].

There is description of the decompensation of the clinical status in patients with hyperammonemia and hepatic lesions in the clinical presentation of a possible
The physical neurological exam, the most consistent findings relate to the involvement of the upper motor neuron. This presentation was present in up to 80% of the cases. The neurologists may note the loss of voluntary motor abilities and the hyperreflexia. The athetosis and ataxia are less frequent [14].

It was reported that the guadinic compounds caused considerable inhibitions of the sodium-potassium-ATPase pump in the cerebral cortex. This is associated to a harmful effect in the CNS [19]. The compounds as the arginine, N-acetylarginine, homoarginine and argininic acid lead to the generation of free radicals. These compounds consequently decrease the antioxidant defenses. They change the catalase enzyme, dismutase superoxide and peroxidase glutathione. These enzymes are the main enzymatic defenses in the brain, contributing to the neurological dysfunction [20,21].

A severe elevation of guanidine compounds presents potential neurotoxic. Tests in vivo and in vitro point to the possibility of inhibition of some inhibitory gamma-aminobutyric acid (GABA) neurotransmitter canals [21].

The induction of seizures may also occur by decreasing the fluidity of plasmatic membrane of the neurons in CNS [22]. Studies also suggest that arginine decreases the activity of the acetylcholinesterase and the kinase creatine [23,24]. This effect damages the respiratory chain and compromises the memory function [24].

The arginine reduces the hydrolysis of the ATP, of the ADP, the AMP and the activity of the butyrycholinesterase in the blood [25-27]. These changes may be prevented by giving the L-NAME (L-NG-Nitroarginine methyl ester). This is an inhibitor of nitric oxide enzyme synthase, provoking the nitric oxide to be involved in these effects [28]. In more advanced cases of the illness, it may also occur cerebellar and brain atrophy. Moreover, it can occur the attack in the posterior portions of the putamen nucleus [29]. These main clinical symptoms can be summarized in Figure 2.

**Diagnosis**

The diagnosis can be confirmed through laboratorial analyses with high concentrations of arginine in the plasma or in the liquor. This exam shows the defect of the arginase enzyme I. The plasmatic concentration of arginine may reach 1.5 Mm. There are data showing that in the cerebrospinal fluid, the values may be 10 times higher than the average value in plasma. The average plasmatic value varies from 21.8 to 87.8 µM and the average liquorice value is 6.8 µM [30-32].

The diagnosis may be confirmed in the pre-natal period. By the analyses of the amniotic fluid and chorionic villi, the genetic analyzes can be performed to find arginase 1 gene (ARG1) mutations [2].

---

**Figure 2:** The Hyperargininemia generates high arginine and ammonia concentration in liquor and brain. This dysfunction generates the neurological symptoms.
One scientific article emphasizes the possibility and importance of establishing a national neonatal screening policy to ensure early detection of inherited metabolic disorders. This research suggests this goal in metabolic diseases which can be easily treated, such as hyperargininemia [33].

In this metabolic disturb, many components from the guanidine accumulate in the blood and in the liquor. The guanidine acetate is a major factor in the development of many physiopathology unbalance. This compound has an epileptic potential in CNS [34].

The nitric oxide and the homoaarginine are also involved in the physiopathology of the illness. The nitric oxide, for example, is formed from the arginine under the nitric oxide synthase. It generates a free radical that may interact with the superoxide and bring to the formation of the peroxynitrite anion. This anion is highly cytotoxic [35].

With the development of the Illness, the increase of level of guanidine compounds settle with the secondary biochemical path activation. The arginine, in high concentrations, is converted into α-acetic-δ-guanidine acid valeric by transamination. This compound forms the arginine acid by hydrogenation. The arginine may also be converted into N-acetyl arginine by acetylation and acetic guanidine acid, β-guanidine butyric by transamination. Yet the homoaarginine, may be formed from the lysine by guanidination [3,35].

The magnetic resonance image (MRI) of the brain may show abnormalities. The main dysfunctions are the brain and cerebellar atrophies. Hyperargininemia can generates lesions in posterior portions of the putamen nucleus. These lesions occur in patients with advanced stages of neurological lesions in hyperargininemia. It hardly ever occurs in patients with lighter degrees of CNS damage in this disease. The high relation choline/creatinine may indicate a deposition of arginine in the nervous tissue [29,36].

The histological evaluation of extracted biopsies from the liver of the hyperargininemia patients tend to show a low degree of fibrosis. However, anatomopathological studies reveal that the patients who develop hyperammonemia tend to show a higher degree of hepatic fibrosis associated to the atrophy of the CNS [14].

Genetic Aspects

The hyperargininemia is characterized by an autosomal recessive genetic origin linked to the chromosome 6 (in the long arm) and to the ARG1 gene. Without a screening test, right after the birth or as soon as possible, the diagnosis becomes more difficult. The illness presents an almost asymptomatic characteristic in the early years [37,38].

The genetic analyses by amplification of the chain reaction of the polymerases already makes it possible to find mutations in ARG1. A study identified five mutations in the ARG1. This laboratorial technique detailed the location of the genetic changes in the chromosome 6 on hyperargininemia [38]. Researchers identified mutations in the gene ARG1 in Brazil. The most frequent mutation in the Brazilian patients analyzed was the p. T1341 [39].

Besides the main gene studied, there is the ARG2 gene. When it is expressed, it produces the formation of arginase enzyme II. This enzyme is found in the kidneys and prostate. However, even with the similar bimolecular characteristic, the function of this enzyme is still not fully understood. The relation of its deficiency and the appearance of the hepatic steatosis is submitted to more evidences. It is now not known if the mutations unitarily in the ARG2 gene may lead to hyperargininemia [40,41].

Experimental studies suggest that the low levels of arginase 1 (as low as 10%) would already be enough to avoid the plasmatic unbalance of hyperargininemia. This could provide a survival of the patients [42].

The gene therapy appears to be promising and useful to avoid the development of the illness, as its neuropathological effects. Arginase 1 gene therapy using adeno-associated virus rescued nearly all these abnormalities when administered to neonatal homozygous knock-out animals. Therefore, gene therapeutic strategies can reverse physiological and anatomical markers of arginase 1 deficiency and therefore may be of therapeutic benefit for the neurological disabilities in this syndrome. With neonatal administration of adeno-associated virus expressing arginase, there is near-total recovery of the abnormalities in neurons and cortical circuits [43].

In 2012, it was developed a learning algorithm, which selects sequences of an informative gene database. This algorithm shows the synthesis of the genes selected. It was created a set of informative of seven chimeras enzymatically active, with portions containing mutation close to the original arginase. This study provided greater understanding about the stability in the long term of the arginase 1. The arginase 1 deactivation in physiological conditions was better understood and its possible therapeutic use in the hyperargininemia patients [44].

Treatment

The treatment consists in a controlled diet. The diet limits the excess of arginine. The frequent medical support is also important. The administration of pharmacological treatment (like benzoate and phenylbutyrate) brings benefits. Some patients present reduction of argininemia. Not all patients respond well to the treatment, but a relevant portion present efficient decrease in the neurological damages and improvement in the clinical state [2].

Patients treated and supervised since birth with controlled and limited protein diet and with supplementa-
tion of essential amino acids tend to present practically asymptomatic. The clinical manifestation is more evident in comparison to the patients who had the diagnosis for more than 30 years [45].

There are few reports of patients who needed the withdrawal of the nitrogen. This treatment is administrated by intravenous route after acute neurological symptoms in hyperargininemia patients. This portion represents a minority among the all patients [46].

An alternative treatment to the disturb is the use of drugs which increase the renal excretion of nitrogen by hippuric acid or phenylacetylglutamine. These options can be cited by sodium benzoate (250-375 mg/Kg/day), L-carnitine (100 mg/Kg/day) and even glycerol phenylbutyrate. It has been demonstrated that the treated patients with this drugs since birth, showed asymptomatic for long periods [47].

In a pediatric study, it showed the effectiveness potential of sodium benzoate given by seven months to a diagnosed child with hyperargininemia. This patient presented spastic paraparesis, ataxia and electroencephalograph abnormalities. The child presented improvement and stabilization of the levels of arginine and ammonia. The patient had a light cognitive deterioration [48].

Patients with secondary seizure to hyperammonemia in the hyperargininemia were treated efficiently with anticonvulsants. These drugs are an efficient option in this disease [16].

The available treatment is a first option to the stabilization of the disease. The reduction of the neurological symptoms and the decrease of the levels of arginine and ammonia are essential [49,50].

Conclusion

The hyperargininemia is an innate dysfunction of the urea cycle caused by the deficiency in the activity of the arginase 1. This enzyme is responsible of the conversion of arginine in urea and ornithine. This illness is biochemically characterized by high levels of arginine and arginine tissue accumulation of guanidino compounds.

The hyperargininemic patients may present a progressive state of spastic tetraplegia, growth restriction, seizures, hyperactivity and hepatomegaly. The neurological lesions generally occur in a progressive way. The patient can be diagnosed with spasticity, ataxia, hypoflexia, motor incoordination, paresis, bilateral Babinski sign, shiver and seizures.

Even being rare, the hyperargininemia is treatable and the therapeutic consists in reducing the levels of plasmatic arginine. The advisable treatment consists in poor diet of natural proteins (restricted in arginine). This approach is supplemented with sodium benzoate and L-carnitine, once the protein restriction isolated is not enough to uniform the levels of arginine.

Our expectation for the future is a further update on the disease by health professionals. Knowing how to perform the diagnosis and recognize early onset in children can change the patient’s life of hyperargininemia. New researches for the development of a more effective treatment may be carried out in the future to bring better quality of life for patients with diseases such as hyperargininemia.

Conflict of Interest

There is no conflict of interest in the present work and the authors did not obtain any financial support to its accomplishment.

References

1. Lehninger AL, Nelson KY (2006) Principles of Biochemistry. 4. ed. São Paulo: Sarvier, 2006.
2. Amayreh W, Meyer U, Anibh M Das (2014) Treatment of arginase deficiency monitoring. Dev Med Child Neuro 56: 1021-1024.
3. Brusilow SW, Maestri NE (1996) Urea cycle disorders: Diagnosis, pathophysiology, and therapy. Adv Pediatr 43: 127-170.
4. Carvalho DR, Brum JM, Speck-Martins CE, Ventura FD, Navarro MM, et al. (2012) Clinical features and neurologic progression of hyperargininemia. Pediatr Neurol 46: 369-374.
5. Batshaw ML, Roan Y, Jung AL, Rosenberg LA, Brusilow SW (1980) Cerebral dysfunction in asymptomatic carriers of ornithine transcarbamylase deficiency. N Engl J Med 302: 482-485.
6. Naylor EW (1981) Newborn screening of urea cycle disorders. Pediatrics 68: 453-457.
7. Naylor EW, Orfanos AP, Guthrie R (1977) A simple screening test for arginase deficiency (hyperargininemia). J Lab Clin Med 99: 876-880.
8. Nagata N, Matsuda I, Oyanagi K (1991) Estimated frequency of urea cycle enzymopathies in Japan. Am J Med Genet 39: 228-229.
9. Scaglia F, Lee B (2006) Clinical, biochemical, and molecular spectrum of hyperargininemia due to arginase I deficiency. Am J Med Genet Part C Semin Med Genet 142: 113-120.
10. Terheggen HG, Schwenk A, Lowenthal A (1969) Arginase deficiency. Lancet 2: 748-749.
11. Qureshi IA, Letarte J, Ouellet R, Larochelle J, Lemieux B (1983) A new French-Canadian family affected by hyperargininaemia. J Inherit Metab Dis 6: 179-182.
12. B Lemieux, Auray-Blais R, Gigudère D, Shacott CR, Sriver (1988) Newborn urine screening experience with over one million infants in the Quebec network of genetic medicine. J Inherit Metab Dis 11: 45-55.
13. Crombez EA, Cederbaum SD (2005) Hyperargininemia due to liver arginase deficiency. Mol Genet Metab 84: 242-251.
14. De Deyn PP, Marescau B, Qureshi IA (1997) Hyperargininemia: A treatable inborn error of metabolism? In: De Deyn PP, Marescau B, Qureshi IA, Mori A, Guanidino Compounds in Biology and Medicine. John Libbey & Company Ltd.,
15. Picker JD, Puga AC, Levy HL, Marsden D, Shih VE, et al. (2003) Arginase deficiency with lethal neonatal expression: Evidence for the glutamine hypothesis of cerebral edema. J Pediatr 142: 349-352.

16. Grioni D, Furlan F, Canonico F, Parini R (2014) Epilepsia partialis continua and generalized nonconvulsive status epilepticus during the course of argininaemia: a report on two cases. Neuropediatrics 45: 123-128.

17. Christmann D, Hirsch E, Mutschler V, Collard M, Marescaux C, et al. (1990) Late diagnosis of congenital argininaemia during administration of sodium valproate. Rev Neurol (Paris) 146: 764-766.

18. Braga AC, Vilarinho L, Ferreira E, Rocha H (1997) Hyperargininaemia presenting as persistent neonatal jaundice and hepatic cirrhosis. J Pediatr Gastroenterol Nutr 24: 218-221.

19. da Silva CG, Parolo E, Streck EL, Wagner M, Wannmacher CM, et al. (1999) In vitro inhibition of Na+,K(+)-ATPase activity from rat cerebral cortex by guanidino compounds accumulating in hyperargininaemia. Brain Res 838: 78-84.

20. Wyse AT, Bavaresco CS, Hagen ME, Delwing D, Wannmacher CM, et al. (2001) In vitro stimulation of oxidative stress in cerebral cortex of rats by the guanidino compounds accumulating in hyperargininaemia. Brain Res 923: 50-57.

21. De Deyn PP, Marescaux C, Macdonald RL (1991) Guanidino compounds that are increased in hyperargininaemia inhibit GABA and glycine responses on mouse neurons in cell culture. Epilepsy Res 8: 134-141.

22. Hiramatsu M, Ohba S, Edamatsu R (1992) Effect of guanidino compounds on membrane fluidity of rat synaptosomes. In: de Deyn BM PP, Stalon V, Qureshi IA, Guanidino Compounds in Biology and Medicine. John Libbey & Co., Guilford, UK, 387-393.

23. Wyse AT, Stefanello FM, Chiarani F, Delwing D, Wannmacher CM, et al. (2004) Arginine administration decreases cerebral cortex acetylcholinesterase and serum butyrylcholinesterase probably by oxidative stress induction. Neurochem Res 29: 385-389.

24. Delwing D, Comelio AR, Wagner M, Wannmacher CM, Wyse AT (2007) Arginine administration reduces creatine kinase activity in rat cerebellum. Metab. Brain Dis 22: 13-23.

25. Delwing D, Tagliari B, Streck EL, Wannmacher CM, Wagner M, et al. (2003) Reduction of energy metabolism in rat hippocampus by arginine administration. Brain Res 983: 58-63.

26. Delwing D, Tagliari B, Chiarani F, Wannmacher CM, Wagner M, et al. (2006) Alpha-tocopherol and ascorbic acid administration prevents the impairment of brain energy metabolism of hyperargininemic rats. Cell Mol Neurobiol 26: 177-189.

27. Eleonora Araújo dos Reis, Leandro Silvade Oliveira, Marcelo Lazzaron Lamers, Carlos Alexandre Netto, Angela Terezinha de Souza Wyse (2002) Arginine administration inhibits hippocampal Na+,K+-ATPase activity and impairs retention of an inhibitory avoidance task in rats. Brain Res 951: 151-157.

28. Delwing D, Gonçalves MC, Sarkis JJ, Wyse AT (2005) LNAME administration prevents the inhibition of nucleotide hydrolysis by rat blood serum subjected to hyperargininemia. Amino Acids 29: 267-272.

29. Güngör S, Akinci A, Firat AK, Tabel Y, Alkan A (2008) Neuroimaging findings in hyperargininemia. J Neuroimaging 18: 457-462.

30. Landsverk ML, Wang J, Schmitt ES, Pursey AN, Wong LJ (2011) Utilization of targeted array comparative genomic hybridization, Mito Met, in prenatal diagnosis of metabolic disorders. Mol Genet Metab 103: 148-152.

31. Snyderman SE, Sansaricq C, Chen WJ, Norton PM, Pan-salkar SV (1977) Argininaemia. J Pediatr 90: 563-568.

32. Fidalgo A, Eusebio F, Tasso T, Pedroso H, I Tavares De Almeida, et al. (1997) Hiperargininemia. A Propósito de 3 Casos Clínicos. Acta Pediatr Port 28: 231-235.

33. Bakhiet M, AIAwadi AM, Al Hammad MM, Ali MF, Butti N (2018) A case report of neurological complications owing to lately diagnosed hyperargininemia emphasizing the role of national neonatal screening policies in the kingdom of Bahrain. Medicine (Baltimore) 97: e10780.

34. Lipton SA, Choy YB, Pan ZH, Lei SZ, Chen HS, et al. (1993) A redox-based mechanism for the neuroprotective effects of nitric oxide and related nitroso-compounds. Nature 364: 626-632.

35. Alderton WK, Cooper CE, Knowles R (2001) Nitric oxide synthases: Structure, function and inhibition. Biochem J 357: 593-615.

36. Carvalho DR, Farage L, Martins BJ, Brum JM, Speck-Martins CE, et al. (2014) Brain MRI and magnetic resonance spectroscopy findings in patients with hyperargininemia. J Neuroimaging 24: 155-160.

37. Wu TF, Yang YL (2013) Advances in clinical and molecular genetics studies on argininaemia. Zhongguo Dang Dai Er Ke Za Zhi 15: 954-959.

38. Mohseni J, Boon Hock C, Abdul Razak C, Othman SN, Hayati F, et al. (2014) Novel complex re-arrangement of ARG1 commonly shared by unrelated patients with hyperargininemia. Gene 533: 240-245.

39. Carvalho DR, Brand GD, Brum JM, Takata RI, Speck-Martins CE, et al. (2012) Analysis of novel ARG1 mutations causing hyperargininemia and correlation with arginase I activity in erythrocytes. Gene 509: 124-130.

40. Vockley JG, Jenkinson CP, Shukla H, Kern RM, Grody WW, et al. (1996) Cloning and characterization of the human type II arginase gene. Genomics 38: 118-123.

41. Navarro LA, Wree A, Povero D, Michael P Berk, Akiko Eguchi, et al. (2015) Arginase 2 deficiency results in spontaneous steatohepatitis: a novel link between innate immune activation and hepatic de novo lipogenesis. J Hepatol 62: 412-420.

42. Hu C, Tai DS, Park H, Cantero G, Chan E, et al. (2015) Minimal ureagenesis is necessary for survival in the murine model of hyperargininemia treated by AAV-based gene therapy. Gene Ther 22: 111-115.

43. Lee EK, Hu C, Bhargava R, Ponnusamy R, Park H, et al. (2013) AAV-based gene therapy prevents neuropathology and results in normal cognitive development in the hyperargininemic mouse. Gene Ther 20: 785-796.

44. Romero PA, Stone E, Lamb C, Chantranupong L, Krause Hayati F, et al. (2014) Novel complex re-arrangement of ARG1 commonly shared by unrelated patients with hyperargininemia. Gene 533: 240-245.

45. Liu AC, Inboden KE, Hultcrantz R, Toivonen T, van der Linden M, et al. (2015) Arginase I and II reveal sequence elements important to sta-
gressive spastic paraparesis, cognitive decline, and novel mutation in ARG1 gene. Pediatr Neurol 51: 430-433.

46. Zhang Y, Landau YE, Miller DT, Marsden D, Berry GT, et al. (2012) Recurrent unexplained hyperammonemia in an adolescent with arginase deficiency. Clin Biochem 45: 1583-1586.

47. Batshaw ML, MacArthur RB, Tuchman M (2001) Alternative pathway therapy for urea cycle disorders: Twenty years later. J Pediatr 138: S46-S54.

48. Baranello G, Alfei E, Martinelli D, Rizzetto M, Cazzaniga F, et al. (2014) Hyperargininemia: 7-month follow-up under sodium benzoate therapy in an Italian child presenting progressive spastic paraparesis, cognitive decline, and novel mutation in ARG1 gene. Pediatr Neurol 51: 430-433.

49. Lal V, Khera D, Gupta G, Singh K, Sharma P (2017) A Case of Hyperargininaemia Presenting at Unusually Low Age. J Clin Diagn Res 11: 01-03.

50. Cantero G, Liu XB, Mervis RF, Lazaro MT, Cederbaum SD, et al. (2016) Rescue of the Functional Alterations of Motor Cortical Circuits in Arginase Deficiency by Neonatal Gene Therapy. J Neurosci 36: 6680-6690.