대한 유전성 대사 질환 : 2022;22(1):15~20

종 설

지발형 오르니틴 트랜스카바미라제 결핍증 환자들의 신경학적 예후

[1]영남대학교병원 소아청소년과, [2]경북대학교 어린이병원 소아청소년과

장경미[1] · 황수경[2]

Neurological Outcome of Patients with Late-onset Ornithine Transcarbamylase Deficiency

Kyung Mi Jang, MD, PhD[1], Su-Kyeong Hwang, MD, PhD[2]

[1]Department of Pediatrics, Yeungnam University School of Medicine, Yeungnam University Hospital, Daegu, South Korea
[2]Department of Pediatrics, School of Medicine, Kyungpook National University, Daegu, South Korea

The most common urea cycle disorder is ornithine transcarbamylase deficiency. More than 80 percent of patients with symptomatic ornithine transcarbamylase deficiency are late-onset, which can present various phenotypes from infancy to adulthood. With no regards to the severity of the disease, characteristic fluctuating courses due to hyperammonemia may develop unexpectedly, and can be precipitated by various metabolic stressors. Late-onset ornithine transcarbamylase deficiency is not merely related to a type of genetic variation, but also to the complex relationship between genetic and environmental factors that result in hyperammonemia; therefore, it is difficult to predict the prevalence of neurological symptoms in late-onset ornithine transcarbamylase deficiency. Most common acute neurological manifestations include psychological changes, seizures, cerebral edema, and death; subacute neurological manifestations include developmental delays, learning disabilities, intellectual disabilities, attention-deficit/hyperactivity disorder, executive function deficits, and emotional and behavioral problems. This review aims to increase awareness of late-onset ornithine transcarbamylase deficiency, allowing for an efficient use of biochemical and genetic tests available for diagnosis, ultimately leading to earlier treatment of patients.

Key words: Hyperammonemia, Late-onset disorders, Ornithine transcarbamylase deficiency, Encephalopathy, Neurological manifestation

Introduction

The most common urea cycle disorder is ornithine transcarbamylase (OTC) deficiency[1)]. Prevalence of OTC deficiency is estimated to be 1: 14,000 live births[2)]; with a bias towards earliest and most severe presentation, with an increased occurrence when late-onset (partial deficiency) OTC deficiency is included. In a study conducted on 260 individuals, all of which presented with symptomatic OTC deficiency, 18% had the neonatal-onset disease, and 82% had the late-onset disease[3)]. OTC deficiency is the only urea cycle disorder that is inherited in an X-linked manner[4)].

Corresponding: Su-Kyeong Hwang, MD, PhD
Department of Pediatrics, School of Medicine, Kyungpook National University, 807 Hoguk-ro, Buk-gu, Daegu 41404, South Korea
Tel: +82-53-200-5704, Fax: +82-53-425-6683
E-mail: skhwang@knu.ac.kr

OTC gene is encoded on the Xp11.4 and is expressed in the mitochondrial matrix of the small intestine and liver, with major complications being neurological[5]. In males and females, OTC deficiency can occur as a late-onset disease and can occur as a severe neonatal-onset disease only in males. In the neonatal period, affected hemizygous males typically present with severe hyperammonemia encephalopathy that is often fatal despite vigorous treatment. Hemizygous males and heterozygous females with late-onset OTC deficiency can present various phenotypes in infancy, later childhood, adolescence, or adulthood. With no regard to the severity of the disease, characteristic fluctuating courses due to hyperammonemia may develop unexpectedly and can be precipitated by metabolic stressors such as infection, or protein consumption[2]. Patients often present signs of acute and rapidly progressive encephalopathy, including altered mentality, lethargy, anorexia, vomiting, hyperventilation, hypothermia, seizures, behavioral disturbances, and obtundation at any age from infancy to adulthood. Besides encephalopathy, developmental delay, learning disabilities, intellectual disability, attention-deficit/hyperactivity disorder, and executive function deficits also may be presented. There is relatively little information known about the long-term neurological and cognitive outcomes of ongoing OTC deficiency. Boys with neonatal onset of the disorder perform poorly, with a deficient cognitive outcome and a high frequency of neurological complications[6]. Girls also presented a poor outcome, with cognitive disability reported in 20-40%[2]. Clinical cases in the literature were reviewed with intention of obtaining information on neurological outcomes and management of patients with late-onset OTC deficiency.

Pathophysiology of neurological complications

Ammonia is predominantly produced by the skeletal muscle from amino acid catabolism, and from absorption from the gut[7]. Fig. 1 summarizes precipitating factors contributing to catabolism; hyperammonemia due to OTC deficiency. After a seemingly normal life, a triggering event such as infection, fasting, pregnancy, childbirth, surgery, trauma, chemotherapy, sodium valproate, carbamazepine, salicylates, haloperidol, systemic corticosteroids, or excess protein intake often results in a sudden appearance of hyperammonemia[8-10]. Ammonia is taken up by hepatocytes, metabolized in the urea cycle, and excreted. The rate-limiting step in the urea cycle is carbamoyl phosphate synthase[11]. The product of this reaction, car-

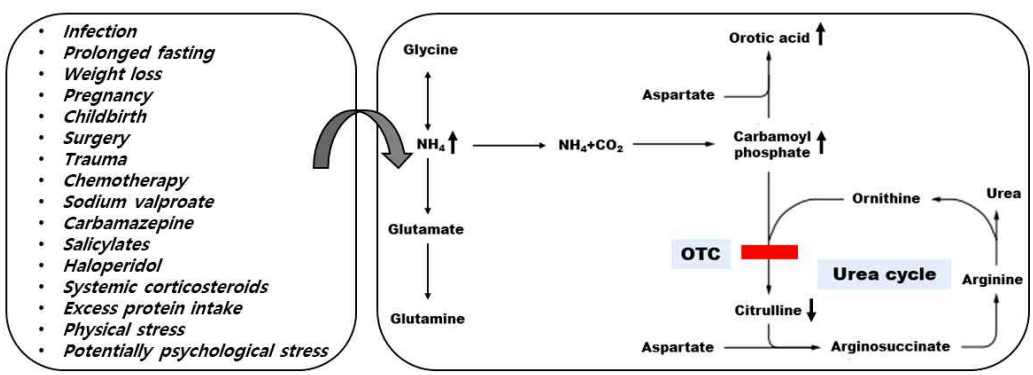

Fig. 1. Precipitating factors contributing to catabolism; hyperammonemia due to OTC deficiency.

bamoyl/phosphate, reacts with OTC to transfer a carbamoyl group to ornithine-producing citrulline. Carbamoyl phosphate is excessively produced during OTC deficiency, with some of this product reacting with aspartate to generate orotic acid, subsequently being excreted through urination. A direct toxic effect on the neurotransmission that is responsible for a portion of the neurological symptomatology is a result of large amounts of proteins being metabolized during the catabolic phase, combined with the effects of ammonia exceeding the urea cycle capacity due to the lack of OTC. Furthermore, the astrocytic glutamine synthetase converts ammonia and glutamate into glutamine, which in turn, acts as an osmolyte and increases cerebral volume, leading to cerebral edema, mental status changes, cerebral engagement, and death[12].

Neurological manifestations

Late-onset OTC deficiency is not merely related to a type of genetic variation, but also to the complex relationship between genetic and environmental factors that result in hyperammonemia; therefore, it is difficult to predict the prevalence of neurological symptoms in late-onset OTC deficiency[13,14]. In a previous study reviewing 30 reported cases of late-onset OTC deficiency from 1987 to 2016, the median age was 37 (age range: 13-67), 57% of individuals being women[11]. The most common acute neurological manifestations included psychological changes, seizures, cerebral edema, and death, with the overall mortality rate being 30%[11]. Subacute neurological manifestations included developmental delays, learning disabilities, intellectual disabilities, attention-deficit/hyperactivity disorder (ADHD), executive function deficits, and emotional and behavioral problems[15,16]. Intelligence scores are related with both peak ammonia levels and with multiple hyperammonemia episodes; therefore, it is difficult to distinguish the difference between the effects of metabolic alterations from hypoxia-ischemia derived, from the cerebral edema[16-19], seeing as both are disease severity indicators. Internalizing problems on the Child Behavior Checklist, such as being withdrawn, depressed, and/or anxious, or having somatic complaints, have also been noted in late-onset OTC deficiency, including in individuals who are "asymptomatic"[15]. With further analysis, it has been revealed that even heterozygous females who have never displayed biochemical evidence of hyperammonemia, present with mild cognitive impairments and deficits in executive function and miniscule motor tasks, despite exhibiting normal IQ on neuropsychological testing. These deficits may only become apparent when individuals are challenged cognitively[20,21].

Brain magnetic resonance imaging findings

Prolonged or frequent hyperammonemia crises are associated with severe impairment of cognitive function and parenchymal injury[22]. Previously, studies have shown that cortical lesions seen on brain magnetic resonance imaging (MRI) of patients with hyperammonemia encephalopathy may either: resolve completely[23], or result in mild atrophy in the cingulate gyrus or insular cortex after treatment[24,25]; thus indicating that early changes are reversible, and suggests the idea that early treatment minimizes, or completely prevents, the neurologic sequelae. Consequently, brain MRI findings may assist with earlier diagnosis of the atypical late-onset OTC deficiency. There is a definite connection between perisulcal lesions and diminished cerebral perfusion in the setting

of elevated intracranial pressure[26]. Pathologically, symmetric cystic lesions at the gray matter–white matter junction, especially in frontal, parietal, hippocampal, and insular regions, are early lesions in patients with hyperammonemia encephalopathy [27,28]. Previously, brain MRIs of late–onset OTC deficiency with severe clinical manifestations demonstrated extensive infarct–like abnormalities involving both cortex and white matter[29-31], presumably due to ischemic lesions in the cerebral intervascular boundary zones[32,33]. In the other study of seven patients with late–onset OTC deficiency (aged 3–27 years), brain MRIs during asymptomatic periods revealed white matter lesions in two patients with an advanced clinical stage; T1 and T2 lesions in the deep white matter and posterolateral angle of the lateral ventricle in one patient; small foci of T2 and T1 prolongation in the subcortical white matter in another[34]. Brain MRI may present as normal in the early stages of the disease, and progress in proportion to the clinical stage; thus, in children, late–onset OTC deficiency should be considered a differential diagnosis of small foci in the white matter[34].

Electroencephalogram

Based on clinical status, patients with late–onset OTC deficiency may need to be monitored with an electroencephalogram (EEG) for differential diagnosis of altered mental status or seizure activity. The EEG in hyperammonemia patients commonly shows a theta activity in the form of mild or latent encephalopathy, with the appearance of increasingly frequent delta waves as the severity of the disease increases[35,36]. During a hyperammonemia coma, the EEG shows low voltage with slow waves and may include a burst suppression pattern in which the duration of the interburst interval correlates with the height of the ammonia levels[37]. Seizures, which may only be detected on an EEG, are common during hyperammonemia and do not indicate a poor prognosis[37].

Conclusion

Late–onset OTC deficiency encompasses a heterogeneous set of conditions. Even in asymptomatic patients with late–onset OTC deficiency, a hyperammonemia crisis can be precipitated by stressors and potentially become a life–threatening event at any stage of life, from infancy, later childhood, adolescence, or adulthood[37]. Delayed diagnosis during the first episode of decompensation may result in death, thus having high suspicion is crucial[38]. Typical neuropsychological manifestations include developmental delay, learning disabilities, intellectual disabilities, ADHD; executive function deficits are present in any individuals with late–onset OTC deficiency[37]. Although affected individuals differed between clinical forms and correlated with lower ammonia levels, the neurological outcomes do not correlate with ammonia levels at diagnosis[38]. This review aims to increase awareness of late–onset OTC deficiency, allowing for efficient use of biochemical and genetic tests available for diagnosis, ultimately leading to earlier treatment of patients.

References

1) Redant S, Empain A, Mugisha A, Kamgang P, Attou R, Honore PM, et al. Management of late onset urea cycle disorders–a remaining challenge for the intensivist? Ann Intensive Care 2021;11:2.
2) Maestri NE, Brusilow SW, Clissold DB, Bassett SS. Long–term treatment of girls with ornithine transcarbamylase deficiency. N Engl J Med 1996;335:855–9.
3) Batshaw ML, Tuchman M, Summar M, Seminara J, Members of the Urea Cycle Disorders C. A longitu-

dinal study of urea cycle disorders. Mol Genet Metab 2014;113:127-30.
4) Waisbren SE, Gropman AL, Members of the Urea Cycle Disorders C, Batshaw ML. Improving long term outcomes in urea cycle disorders-report from the Urea Cycle Disorders Consortium. J Inherit Metab Dis 2016;39:573-84.
5) Nicolaides P, Liebsch D, Dale N, Leonard J, Surtees R. Neurological outcome of patients with ornithine carbamoyltransferase deficiency. Arch Dis Child 2002; 86:54-6.
6) Maestri NE, Clissold D, Brusilow SW. Neonatal onset ornithine transcarbamylase deficiency: A retrospective analysis. J Pediatr 1999;134:268-72.
7) Walker V. Ammonia toxicity and its prevention in inherited defects of the urea cycle. Diabetes Obes Metab 2009;11:823-35.
8) Haberle J, Burlina A, Chakrapani A, Dixon M, Karall D, Lindner M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis 2019;42:1192-230.
9) Hidaka M, Higashi E, Uwatoko T, Uwatoko K, Urashima M, Takashima H, et al. Late-onset ornithine transcarbamylase deficiency: a rare cause of recurrent abnormal behavior in adults. Acute Med Surg. 2020; 7:e565.
10) Nassogne MC, Heron B, Touati G, Rabier D, Saudubray JM. Urea cycle defects: management and outcome. J Inherit Metab Dis 2005;28:407-14.
11) Pizzi MA, Alejos D, Hasan TF, Atwal PS, Krishnaiengar SR, Freeman WD. Adult Presentation of Ornithine Transcarbamylase Deficiency: 2 Illustrative Cases of Phenotypic Variability and Literature Review. Neurohospitalist 2019;9:30-6.
12) Wijdicks EF. Hepatic Encephalopathy. N Engl J Med 2016;375:1660-70.
13) Arranz JA, Riudor E, Marco-Marin C, Rubio V. Estimation of the total number of disease-causing mutations in ornithine transcarbamylase (OTC) deficiency. Value of the OTC structure in predicting a mutation pathogenic potential. J Inherit Metab Dis 2007;30: 217-26.
14) Krivitzky L, Babikian T, Lee HS, Thomas NH, Burk-Paull KL, Batshaw ML. Intellectual, adaptive, and behavioral functioning in children with urea cycle disorders. Pediatr Res 2009;66:96-101.
15) Waisbren SE, He J, McCarter R. Assessing Psychological Functioning in Metabolic Disorders: Validation of the Adaptive Behavior Assessment System, Second Edition (ABAS-II), and the Behavior Rating Inventory of Executive Function (BRIEF) for Identification of Individuals at Risk. JIMD Rep 2015;21:35-43.
16) Buerger C, Garbade SF, Dietrich Alber F, Waisbren SE, McCarter R, Kolker S, et al. Impairment of cognitive function in ornithine transcarbamylase deficiency is global rather than domain-specific and is associated with disease onset, sex, maximum ammonium, and number of hyperammonemic events. J Inherit Metab Dis 2019;42:243-53.
17) Posset R, Gropman AL, Nagamani SCS, Burrage LC, Bedoyan JK, Wong D, et al. Impact of Diagnosis and Therapy on Cognitive Function in Urea Cycle Disorders. Ann Neurol 2019;86:116-28.
18) Batshaw ML. Hyperammonemia. Curr Probl Pediatr 1984;14:1-69.
19) Dolman CL, Clasen RA, Dorovini-Zis K. Severe cerebral damage in ornithine transcarbamylase deficiency. Clin Neuropathol 1988;7:10-5.
20) Sprouse C, King J, Helman G, Pacheco-Colon I, Shattuck K, Breeden A, et al. Investigating neurological deficits in carriers and affected patients with ornithine transcarbamylase deficiency. Mol Genet Metab 2014; 113:136-41.
21) Anderson A, Gropman A, Le Mons C, Stratakis C, Gandjbakhche A. Evaluation of neurocognitive function of prefrontal cortex in ornithine transcarbamylase deficiency. Mol Genet Metab 2020;129:207-12.
22) Msall M, Batshaw ML, Suss R, Brusilow SW, Mellits ED. Neurologic outcome in children with inborn errors of urea synthesis. Outcome of urea-cycle enzymopathies. N Engl J Med 1984;310:1500-5.
23) Kawata A, Suda M, Tanabe H. Adult-onset type II citrullinemia: clinical pictures before and after liver transplantation. Intern Med 1997;36:408-12.
24) Baganz MD, Dross PE. Valproic acid-induced hyperammonemic encephalopathy: MR appearance. AJNR Am J Neuroradiol 1994;15:1779-81.
25) Chen YF, Huang YC, Liu HM, Hwu WL. MRI in a case of adult-onset citrullinemia. Neuroradiology 2001; 43:845-7.
26) Janzer RC, Friede RL. Perisulcal infarcts: lesions caused by hypotension during increased intracranial pressure. Ann Neurol 1979;6:399-404.
27) Martin JJ, Farriaux JP, De Jonghe P. Neuropathology of citrullinaemia. Acta Neuropathol 1982;56:303-6.
28) Filloux F, Townsend JJ, Leonard C. Ornithine transcarbamylase deficiency: neuropathologic changes acquired in utero. J Pediatr 1986;108:942-5.
29) Connelly A, Cross JH, Gadian DG, Hunter JV, Kirkham FJ, Leonard JV. Magnetic resonance spectroscopy shows increased brain glutamine in ornithine carbamoyl transferase deficiency. Pediatr Res 1993;33: 77-81.
30) Bajaj SK, Kurlemann G, Schuierer G, Peters PE. CT

and MRI in a girl with late-onset ornithine transcarbamylase deficiency: case report. Neuroradiology 1996;38:796-9.
31) de Grauw TJ, Smit LM, Brockstedt M, Meijer Y, vd Klei-von Moorsel J, Jakobs C. Acute hemiparesis as the presenting sign in a heterozygote for ornithine transcarbamylase deficiency. Neuropediatrics 1990;21:133-5.
32) Mirowitz SA, Sartor K, Prensky AJ, Gado M, Hodges FJ, 3rd. Neurodegenerative diseases of childhood: MR and CT evaluation. J Comput Assist Tomogr 1991;15:210-22.
33) Mamourian AC, du Plessis A. Urea cycle defect: a case with MR and CT findings resembling infarct. Pediatr Radiol 1991;21:594-5.
34) Kurihara A, Takanashi J, Tomita M, Kobayashi K, Ogawa A, Kanazawa M, et al. Magnetic resonance imaging in late-onset ornithine transcarbamylase deficiency. Brain Dev 2003;25:40-4.
35) Amodio P, Marchetti P, Del Piccolo F, de Tourtchaninoff M, Varghese P, Zuliani C, et al. Spectral versus visual EEG analysis in mild hepatic encephalopathy. Clin Neurophysiol 1999;110:1334-44.
36) Brunquell P, Tezcan K, DiMario FJ, Jr. Electroencephalographic findings in ornithine transcarbamylase deficiency. J Child Neurol 1999;14:533-6.
37) Lichter-Konecki U, Caldovic L, Morizono H, Simpson K, Ah Mew N, MacLeod E. Ornithine Transcarbamylase Deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Gripp KW, et al., editors. GeneReviews((R)). Seattle (WA) 1993.
38) Brassier A, Gobin S, Arnoux JB, Valayannopoulos V, Habarou F, Kossorotoff M, et al. Long-term outcomes in Ornithine Transcarbamylase deficiency: a series of 90 patients. Orphanet J Rare Dis 2015;10:58.