A Female with X-linked Ornithine Transcarbamylase Enzyme Deficiency (Case Report)

Mo'men O. Alakil*, MD, Noor A. Megdadi, MD, Mai N. Almaseed, MD, Duaa A. Alhlasy,MD, Shahrazad M. Qayyam,MD, Moshera A. Al Dwari, RN, Jalaa' M. Talfha, RN

ABSTRACT

Inborn errors of metabolism (IEM) are collectively quite common disorders and they usually have an autosomal recessive inheritance pattern. X-linked recessive diseases are less common and they affect the male gender mostly. If a male has a mutant gene on the X chromosome, it will express a phenotype, as there is no normal allele. On the other hand, females with a healthy allele will not express the disease. In rare cases and due to the Lyonization phenomenon of the X chromosome in females, a mutant allele can express a disease if it lyonized over the healthy one. In these rare cases of females affected with an X-linked recessive disease, the disease usually presents mild or intermittent. Therefore the diagnosis would be challenging. Our case is about a 2-year-old female with ornithine transcarbamylase (OTC) enzyme deficiency. OTC is one of the urea cycle enzymes coded on the X chromosome and usually presents with hyperammonaemic encephalopathy.

Keywords: X-linked inheritance; urea cycle disease; ornithine transcarbamylase (OTC) enzyme deficiency; Jordan.

RMS April 2021; 28(1): 10.12816/0058883

Introduction

Inherited metabolic disorders are in general not rare, with urea cycle disorders being the most common group of inborn errors of metabolism (IEM). Ornithine transcarbamylase (OTC) deficiency is the most common urea cycle disorder (1-3). The urea cycle is the primary pathway to detoxify ammonia to supply arginine in our bodies (4). OTC deficiency is the only X-linked recessive disorder that may affect the urea cycle enzymes (5). The phenotype of the diseased males usually depends on the genetic mutation site; mutations around the active site of the enzyme present with severe signs and early in life, while other mutations away from the active site of the enzyme present later and less severe (6,7).

Hyperammonemia from urea cycle disorders usually presents with a wide spectrum of non-specific symptoms, such as vomiting, lethargy, hepatopathy, hypertension, abnormal behaviour, mental retardation, blindness, spasticity, seizures and coma (8-10). Heterozygous females are mostly asymptomatic, with approximately only 15% developing symptoms during their lives.

From the departments of:
Pediatrics medicine
Correspondence should be addressed to: Dr.

These symptoms are usually mild and intermittent, and less than 25% of those who are symptomatic may develop hyperammonaemic coma. (3, 11-13). The incidence of all urea cycle diseases as in *Summer,et al* (5) is 1/35,000 and OTC deficiency is the most common one with an incidence of 1/56,500.

Case report:

This is a case of a 2-year-old female patient who was delivered normally in a private hospital in Amman, Jordan at 37-weeks gestational age. Her birth weight was 3kg, and she was discharged home after 36 hours of observation. She is the second baby of non-related parents. She has a 4-year-old healthy sister. The patient was on breast milk feeding in her first month of life and then a regular formula was added. She was growing and developing normally, and she received her vaccines according to the Jordanian national programme. When she was 23 months old, her parents noticed that she started to be irritable with diarrhoea, with a frequency of approximately four times a day. She was treated for presumed acute gastroenteritis, but her symptoms progressed. She developed ataxic gait, abnormal behaviour, tonic-clonic seizures, and lastly sudden vision loss. Her parents took her to a private hospital where she was treated for presumed acute encephalitis and then as autoimmune encephalitis without significant improvement. After a month of hospitalization, she developed hepatomegaly. Her laboratory blood tests showed coagulopathy, hypoalbuminaemia, elevated transaminases, and elevated ammonia. At this stage, she was transferred to Queen Rania Al-Abdullah Hospital for Children. Her initial exam was the same as above. Her laboratory investigations initially and on regular follow ups, are shown in Table (1).

Table (I): Baseline and follow up laboratory results.

Test	Day 0	Day 3	Day 7	Day 15	Day 90	Day 180	Day 270
ALT (IU/l)	294	492	556	36	29.5	The patient missed her clinic appointment due to COVID-19 pandemic curfew	31
AST (IU/l)	200	294	441	32	53.7		38
Albumin (g/dl)	4.8	4.04	4.6	4.93	4.27		4.5
Total protein (g/dl)	6	5.64	5.9	6.41	6.33		7
PT (second)	22.4	20.2	-	12.3	14.7		14.7
INR	1.75	1.52	-	0.92	1.09		1.09
PTT (second)	29.9	31.6	-	20.1	29.7		29.7
Ammonia (µg/dl)	644	12	432	16.3	139.8		113
Lactate (mg/dl)	18	26.4	29	18.4	33.8		15

Radiographic studies were reviewed. There was hepatomegaly on abdominal ultrasound with normal echotexture, normal brain CT scan, and normal brain MRI. At this stage the differential diagnosis included autoimmune hepatitis, autoimmune encephalitis, metabolic liver disease, neurometabolic disorder and urea cycle disorder. Therefore a metabolic workup, including serum aminoacids, urine organic acids, and acylcarnitines, was sent to the laboratory, and the patient was started on a protein-restricted diet with ammonia scavengers and l-arginine supplements. Her symptoms improved by this management. Her vision returned within a week, and her gait returned to normal after 3 weeks. Her ammonia level, surprisingly, returned to lower than the normal ranges after 3 days, and the ammonia scavengers were stopped. Unfortunately, her ammonia level rose again to four times above the upper normal range, and the patient again started to have abnormal behaviour. Thereafter, ammonia scavengers were restarted, with better clinical results according to her symptoms and general physical exam. On the other hand, the metabolic screen was normal on three occasions, so whole exome sequencing (WES) was used for the diagnosis. WES was performed in a private laboratory, which was positive for a splicing mutation, class 1 pathogenic, heterozygous, NM_000531.5:c.1006-1G>A on the OTC gene on the X chromosome, which confirmed the diagnosis of X-linked OTC deficiency (7).

The patient is now maintained on a protein-restricted diet, ammonia scavengers and l-arginine supplements. She is regularly followed at the Metabolic Clinic and her clinical course is improving.

DISCUSSION

This case illustrates the challenges that medical providers face to reach a diagnosis in rare disorders, including IEM and further difficulties that may be met in heterozygous females with X-linked recessive inherited disorders. For example, in the above-mentioned case, hyperammonaemia may present with encephalopathy and hepatopathy. However, hepatopathy, from any other cause, may also present with hyperammonaemia and encephalopathy (9, 10, 14).

A positive history or a positive family history of unexplained recurrent illnesses or deaths usually increases the suspicious of IEM. Laboratory biochemical findings such as hyperammonemia, hyperlactatemia, abnormal serum aminoacid profile, abnormal findings in the acylecarnetins and the newborn screening tests and abnormal organicacids in the urine in most cases narrow the differential diagnosis of a physician sometimes make a specific diagnosis. Functional dietary, exercise and other tests challenging a pathway of a metabolite can also help. Confirmed IEM diagnosis is reached via specific enzymatic assay or genetic mutation detection. (18).

The hallmark of urea cycle disorders is hyperammonimic encephalopathy, therefore any patient who is suspected to have hyperammonemia should be treated urgently. The principles of emergency treatment include; exogenous protein restriction with argenine supplements (argenine is contraindicated if arginase deficiency is suspected), ensure high energy supply from lipids and carbohydrates and ammonia reduction pharmacologically or with dialysis. Maintenance management depends on the specific diagnosis. Dietary protein restriction to the recommended daily requirement according to FAO/WHO is useful with vitamins and trace elements supplements to avoid dietary deficiencies. Hyperammonemia can be managed with ammonia scavengers such as sodiumbenzoate , sodium phenylbuterate and glycerol phenylbuterate. Carglumic acid ,which stimulates the urea cycle, is curative in cases of NAGS deficiency and it can stimulate the urea cycle. L-argenine and l-citrulline supplements stimulate the residual function of the urea cycle. (9, 10)

Summer,et al (5) summarized the incidence of the urea cycle disorders as shown in table (II).

Table II: The incidence of all urea cycle disorders.

All UCDs		**1/35,000**	
NAGS	<1/2,000,000	**ASL**	1/218,750
CPS1	1/1,300,000	**ARG**	1/950,000
OTC	1/56,500	**Citrin**	<1/2,000,000
ASS	1/250,000	**HHH**	<1/2,000,000

ARG: Arginase deficiency, ASL: Arginosuccinate layase deficiency, ASS: Arginosuccinate synthetase deficiency, CPS1: Carbomylphosphatase 1 deficiency, Citrin: Aspartate/Glutamate antiporter deficiency, HHH: Hyperammonemia/Hyperornithinemia/Homocitrulinemia syndrome, NAGS: N-acetylglutamate synthase deficiency, OTC: Ornithine transcarbamylase deficiency, UCDs: Urea cycle disorders.

OTC deficiency is the most common urea cycle disorder, which is usually fully expressed in newborn males and expressed in variable severities in heterozygous females. The wide range of presentations in females that are heterozygous carriers makes the diagnosis challenging, especially without a positive family history or a previously affected sibling. Symptoms range from lethal newborn presentation to asymptomatic carriers whose symptoms appear only with stressful situations, such as acute illness, surgery, or vaginal delivery (3, 12). Thereafter, the differential diagnosis of OTC deficiency in females is delayed in most cases, as in the above-mentioned case.

As Pinto *et al.* (15), both mucopolysacharidosis II (MPS II) and fabry disease are X-linked disorders that show wide spectrum expression in heterozygous females. It is thought that these differences could be explained by cross-correction mechanisms and skewed X-inactivation.

The X chromosome lyonization phenomenon leads to mosaic cells, i.e. some cells with a non-mutant X chromosome and others with a mutant one). This mosaic usually leads to biological advantages, but with no guarantee of this (15, 16).

Although the X-inactivation mechanism was discovered about 50 years ago, X-linked diseases show a continuum of penetrance pattern due to an unclear mechanism, which requires further scientific information about cell biology to allow us to provide better informed genetic counselling to affected families (17).

Conclusion

Physicians find rare disorders, in general, difficult to diagnose due to their unusual presentations and the need for specific laboratory investigations. Newborn screening programmes can be manipulated for each country according to the disease prevalence, available treatment options and the severity at presentation. Awareness of other IEMs, which were not included in screening programmes, missed in the screening programme and/or were normal at screening, should be increased among general physicians and paediatricians in order to make a rapid diagnosis and start treatment, so as to ensure better outcome. On the other hand, unsolved cases and patients with unusual presentations or disease progression should be referred to specialized centres that can deal with these patients. Genetic assessment and diagnosis are nowadays mandatory to establish the diagnosis and to offer better counselling to the family.

Acknowledgment

We would like to express our great appreciation and gratitude to both parents who permitted us to publish their daughter's case and to the officials at Queen Rania Al-Abdullah Hospital for Children for their effort collecting and analysing the data for this case study.

REFERENCES

1) **Nagata, N., Matsuda, I., Oyanagi, K.** (1991). Estimated frequency of urea cycle enzymopathies in Japan. *American Journal of Medical Genetics, 39*, 228–229.
2) **Brusilow, S., & Maestri, N. E.** (1996). Urea cycle disorders: Diagnosis, pathophysiology, therapy. In L. A. Barness, D. C. DeVivo, M. M. Kaback, G. Morrow, F. A. Oski, & A. M. Rudolph (Eds.), *Advances in paediatrics* (p.127). Chicago: Mosby.
3) **Gyato, K, Wray, J, Huang, Z. J.,Yudkoff, M., & Batshaw, M. L.** (2004). Metabolic and neuropsychological phenotype in women heterozygous for ornithine transcarbamylase deficiency. *Annals of Neurology, 55*, 80–86.
4) **Walker, V.** (2009). Ammonia toxicity and its prevention in inherited defects of the urea cycle. *Diabetes, Obesity and Metabolism, 11*, 823–835.
5) **Summar, M. L., Koelker, S., Freedenberg, D., et al.** (2013). The incidence of urea cycle disorders. *Molecular Genetics and Metabolism, 110*, 179–180.
6) **Caldovic, L., Abdikarim, I., & Narain, S.** (2015). Genotype-phenotype correlations in ornithine transcarbamylase deficiency: A mutation update. *Journal of Genetics and Genomics, 42*, 181–194.
7) **McCullough, B., Yudkoff, M., & Batshaw ML.** (2000). Genotype spectrum of ornithine transcarbamylase deficiency: Correlation with the clinical and biochemical phenotype. *American Journal of Medical Genetics, 93*, 313–319.
8) **Häberle, J., Boddaert, N., Burlina, A., et al.** (2012). Suggested guidelines for the diagnosis and management of urea cycle disorders. *Orphanet Journal of Rare Diseases, 7*, 32.
9) **Häberle, J., Burlina, A., Chakrapani, A., et al.** (2019) Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. *Journal of Inherited Metabolic Disease, 42*, 1192–1230.
10) **Häberle, J., & Rubio, V.** (2016). Disorders of the urea cycle and related enzymes. In J.M. Saudubray,M. Baumgartner, & J. Walter (Eds.),*Inborn metabolic diseases*(pp. 295-308).Berlin: Springer-Verlag.
11) **Meastri, N. E., Lord, C., Glynn, M., Bale, A., & Brusilow, S. W.** (1998). The phenotype of ostensibly healthy women who are carriers for ornithine transcarbamylase deficiency. *Medicine, 77*, 389–397.
12) **Ahrens, M.J., Berry, S. A., Whitley, C. B., Markowitz, D. J., Plante, R. J., & Tuchman M.** (1996). Clinical and biochemical heterogeneity in females of a large pedigree with ornithine transcarbamylase deficiency due to the R141Q mutation. *American Journal of Medical Genetics, 71*, 311–315.
13) **Batshaw, M. L., Roan, Y., Jung, A. L., Rosenberg L. A., & Brusilow, S. W.** (1980). Cerebral dysfunction in asymptomatic carriers of ornithine transcarbamylase deficiency. *New England Journal of Medicine, 302*, 482–485. http://dx.doi.org/10.1056/NEJM198002283020902
14) **Khan, A., Ayub, M.,&Khan, W. M.** (2016).Hyperammonemia isassociated with increasing severity of both liver cirrhosis and hepatic encephalopathy.*International Journal of Hepatology, 2016*, 6741754. http://dx.doi.org/10.1155/2016/6741754
15) **Pinto, L. L., Vieira, T. A., Giugliani, R., & Schwartz, I. V.** (2010). Expression of the disease on female carriers of X-linked lysosomal disorders: a brief review.*Orphanet Journal of Rare Diseases, 5*, 14. http://dx.doi.org/10.1186/1750-1172-5-14

16) **Uehara, S., Hashiyada, M., Sato, K., Sato, Y., Fujimori, K., &Okamura, K.** (2001). Preferential X-chromosome inactivation in women with idiopathic recurrent pregnancy loss. *Fertility and Sterility, 76*, 908–914.
17) **Dobyns, W. B., Filauro, A., Tomson, B. N., Chan, A. S., Ho, A. W., Ting, N. T., et al.** (2004). Inheritance of most X-linked traits is not dominant or recessive, just X-linked. *American Journal of Medical Genetics Part A, 129A*, 136–143.
18) **Häberle, J., & Rubio, V.** (2016). Diagnostic procedures. In J.M. Saudubray, M. Baumgartner, & J. Walter (Eds.), *Inborn metabolic diseases*(pp. 91-109).Berlin: Springer-Verlag.