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A novel presentation of an ATP1A3 gene mutation – case report and literature review

E. KOSTOPOULOU, A. AVGERI, M.I. APOSTOLOU, S. TZIFAS, G. DIMITRIOU

Department of Pediatrics, NICU, University of Patras Medical School, Patras, Greece

Abstract. – OBJECTIVE: Mutations in the *ATP1A3* gene cause the classical disorders of rapid-onset dystonia-parkinsonism (RDP), alternating hemiplegia of childhood (AHC) and cerebellar ataxia, areflexia, *pes cavus*, optic atrophy, and sensorineural hearing loss (CAPOS). However, intermediate phenotypes have also been described, making the range of clinical manifestations associated with mutations in the *ATP1A3* gene wider. A rare case of an *ATP1A3* gene mutation is presented.

CASE REPORT: Genetic testing was performed in a neonate who presented with neurological abnormalities on day 2 of life, severe electrolytic disturbances a few days later and developmental delay and epilepsy a few months later. A pathogenic heterozygous missense mutation in the *ATP1A3* gene (c.2482G>A, E828K(p.Glu828Lys) was detected on clinical exome sequencing.

CONCLUSIONS: The present case report extends the already described phenotypic variation observed in individuals with *ATP1A3* gene mutations. It also illustrates the importance of genetic testing in the case of complex and not straightforward clinical scenarios, particularly when present from a very young age, before clinical criteria for known diagnoses are met.

Key Words:
ATP1A3 gene, Neonate, Hyporeflexia, Hypotonia, Epilepsy.

Introduction

We report a rare case of a heterozygous mutation in the *ATP1A3* gene and provide a literature review of the clinical phenotypes associated with mutations in this gene. Informed consent was obtained by the parents of the infant described.

The classical spectrum of disorders in relation with mutations in the *ATP1A3* gene includes: i) Rapid-onset dystonia-parkinsonism (RDP), ii) alternating hemiplegia of childhood (AHC) and iii) cerebellar ataxia, areflexia, *pes cavus*, optic atrophy, and sensorineural hearing loss (CAPOS)[1].

RDP, first recognized in 1993, is a non-dopa-responsive dystonia characterized by abrupt, or rarely gradual, onset of dystonia, usually over days to weeks. Parkinsonism in the form of bradykinesia and postural instability, and common bulbar involvement are additional clinical manifestations. Anxiety, depression and seizures may also occur[2]. AHC is a rare neurological disorder that manifests in infancy or early childhood as alternating hemiplegia/hemiparesis or dystonic attacks, quadriparesis, tonic spells, seizure-like episodes and oculomotor abnormalities[3]. CAPOS syndrome presents between the age of 6 months and 4 years old as episodes of ataxic encephalopathy and/or weakness after a febrile illness. Pregnancy can also result in worsening of symptoms[4].

Intermediate phenotypes or few symptoms that do not fit well into the three major phenotypes have also been described. All the related disorders are considered to represent a continuum of phenotypes since the same variant may lead to different phenotypes[1]. At least 83 *ATP1A3* mutations have been described in patients with the aforementioned three disorders[1,5,6].

Case Report

A female neonate, the third child of healthy Caucasian non-consanguineous parents, presented on day 2 of life with lethargy, reduced response to stimuli and mild grumble. No dystonia, episodes of hemiplegia or seizures were witnessed. The neonate was born by caesarean section due to previous caesarean sections at 37 weeks of gestation, after an uneventful pregnancy and an uncomplicated labour. The birth weight was 3180 grams (appropriate for gestational age/AGA) and Apgar score was 9 at 1 minute and 10 at 5 minutes after birth. The perinatal history was unremarkable. Parental history was negative for neurological disorders. The maternal grandfather was diagnosed with Parkinson's disease at the age of

Corresponding Author: Eirini Kostopoulou, MD;
e-mail: irekost@upatras.gr, eirini.kost@gmail.com.

55 years and the neonate's older sibling was diagnosed with benign Rolandic epilepsy two months earlier, at the age of 12 years.

On examination, generalized hypotonia, reduced muscle tone and diminished deep tendon and neonatal reflexes were recognized. There were no dysmorphic features. Acute encephalopathy was suspected. A capillary blood glucose measurement revealed hyperglycaemia (Glucose: 314 mg/dl). Metabolic acidosis was identified on a blood gas (pH: 7.29, HCO_3^-: 13.7, pCO_2: 21.4, BE: -14.2,), as well as increased lactic acid (9.7 mmol/l). CPK was elevated (CPK: 958 U/l), however there was no evidence of perinatal asphyxia. C-reactive protein (CRP) was within the normal range, nonetheless empiric treatment with intravenous ampicillin, cefotaxime and gentamycin, was immediately initiated for presumed sepsis. Acyclovir was also administered. No respiratory distress was observed and a chest radiograph showed no pathology. No other pathology was identified at that time (Table I). The blood culture that was obtained before antibiotics were started came back negative.

On day 3 of life the clinical picture remained unchanged, and a brain and abdominal ultrasound showed no pathology. On electroencephalogram (EEG), no abnormal electric activity was identified. On day 4 of life the neonate was started on extensively hydrolysed infant formula and a metabolic screen was performed to exclude inborn errors of metabolism. Results showed increased 3-Hydroxy-Butyric acid, acetoacetic and 2-ketobutyric acid. Urine organic acid test was repeated on the 21st day of life and was found normal. Plasma aminoacids, lactic acid and carnitine/acylcarnitine profiles were within the normal limits. Results from CSF neurotransmitters and biochemical serum metabolites showed reduction in biogenic amines, 5-Hydroxy-indoloacetic and homovanillic acid (Table I), raising suspicion for tyrosine hydroxylase deficiency. Urine Vanillylmandelic acid (VMA) and beta 2 microglobulin were also normal.

On day 5 of life the neonate developed hyponatremia, hypocalcemia and hyperphosphatemia. Increased urine ketones, glucose, haemoglobin and protein were also detected. The blood gas revealed compensated metabolic acidosis and respiratory alkalosis. Hyponatremia was managed with increased intravenous sodium administration, and subsequently fluid restriction was also applied. It resolved completely 12 days later. Hypocalcemia was managed with intravenous calcium gluconate. Glucosuria and increased urine protein persisted until the 6th day of life.

Extended endocrine investigations were performed (Table II). Neonatal diabetes was excluded as a potential cause of hyperglycaemia. Congenital adrenal hyperplasia, hypoaldosteronism, pseudohypoaldosteronism and SIADH were excluded as primary or supplementary causes of hyponatremia. Of note, the neonate had normal female genitalia. A renal ultrasound-doppler showed normal kidney dimensions and morphology and the renal artery and vein were also normal. Brain MRI showed no remarkable findings.

At the age of 19 days, three brief episodes of rapid, irregular, nonrhythmic eye movements, characterized as opsoclonus, were observed. An ophthalmology examination revealed no abnormality.

During hospitalisation, the neonate's neurological examination slightly improved after the electrolytic disturbances resolved. She became more alert and hyporeflexia improved, however she never achieved a completely normal state of alertness and hypotonia persisted. Furthermore, the neonate exhibited no respiratory distress. Physical examination of the gastrointestinal system was also always normal and weight gain was satisfactory. Urination and renal function tests were continuously normal. A 1/6 systolic cardiac murmur was identified and a cardiac ultrasound revealed a patent foramen ovale and mild to moderate mitral valve regurgitation. Cardiac findings resolved at the age of 23 days. The neonate was discharged after 27 days of hospitalisation in stable clinical condition and with normal laboratory tests.

Currently, at the age of 8 months, the infant is developmentally delayed and low in gaining milestones. She has generalised hypotonia and delayed gross motor skills development with poor head control. Few episodes of opsoclonus have been reported and she has not been started on solid foods due to swallowing difficulties. Up until the age of 5 months she was hospitalised 5 times due to generalized tonic-clonic seizures. She was initially treated with levetiracetam and subsequently switched to double treatment with clonazepam and flunarizine. She has been seizure-free for the last 2 months. She also has a normal hearing test and is under physical therapy, speech therapy and paediatric neurology follow-up.

Genetic testing was performed during hospitalisation. A heterozygous missense mutation in the *ATP1A3* gene c.2482G>A, E828K(p.Glu828Lys) was detected on clinical exome sequencing. The mutation was described as pathogenic[7] and is predicted to be disease causing. Therefore, although the clinical phenotype of the neonate does not fit

in any of the described conditions so far, we presume that the mutation accounts for the neonate's abnormal neurological symptoms and signs, which were worsened by the observed electrolytic disorders. We also hypothesize that the electrolytic disturbances and the abnormal findings on urinalysis were caused by acute tubular acidosis due to aminoglycoside administration, which was initiated on day 2 of life.

Discussion

The classical disorders associated with *ATP1A3* gene mutations, RDP, AHC and CAPOS, demonstrate a wide range of clinical manifestations. In RDP, symptoms are triggered by fever, overheating, physiologic or emotional stress or alcoholic binges[2]. First episodes often stabilize with little improvement, whereas second episodes are characterized by abrupt worsening of symptoms. Besides dystonia and parkinsonism, additional manifestations include mood disorders in 50% of the cases and psychosis in 19% of them[8]. Affected individuals age between 6 months and 59 years old and more than half of the cases are caused by *de novo* mutations[9]. Also, the onset of the disease can occur in infancy, childhood or adulthood and symptoms may be atypical and have variable outcome[9]. Medical treatment for RDP is limited. The disease is unresponsive to Levodopa and symptomatic relief is provided by benzodiazepines in some of the cases[8].

In AHC, the frequency of the episodes is variable, ranging from one episode every few months to multiple episodes per day. Triggers associated with paroxysmal episodes of AHC include psychological stress, bright light, excessive heat or cold, excessive noise, water exposure, excessive exercise, illness, irregular sleep. With the progress of time, persistent neurological abnormalities develop, such as oculomotor apraxia, ataxia, choreoathetosis, dystonia, parkinsonism, autonomic dysfunction and cognitive dysfunction[3]. Epilepsy also develops in more than 50% of the patients. In the majority of the patients the disease starts before the age of 6 months. Plegic and tonic attacks disappear with sleep[10]. Between attacks neurological examination is normal and ataxia, dystonia and other involuntary movements and intellectual disability are common[11]. The prevalence of the disorder is 1:100,000 children[12]. Mutations in the *ATP1A3* gene, which is located at 19q13.2 [hg19], represent the primary cause of AHC, accounting for approximately 75% of cases. The disease is transmitted as an autosomal dominant trait. Most of the mutations are *de novo,* however the disease can also be transmitted to the offspring[13].

In CAPOS syndrome, the neurologic sequelae is progressive and permanent, resulting in gait and limb ataxia and areflexia. Visual impairment due to optic atrophy and sensorineural hearing loss also develop, beginning in childhood. Severity and progression of sensory losses vary. The diagnosis of CAPOS syndrome is established by the identification of a heterozygous pathogenic variant in the *ATP1A3* gene in molecular genetic testing[4].

Another unique clinical phenotype, referred to as D-DEMØ and also caused by mutations in the *ATP1A3* gene, has recently been described in 4 patients. It is characterized by 6 distinct features: dystonia, facial dysmorphism, encephalopathy with developmental delay, cerebellar hypoplasia, no hemiplegia and neonatal onset of symptoms[14].

The *ATP1A3* gene consists of 23 exons and encodes the sodium-potassium (Na^+/K^+) ATPase α3 subunit. The Na^+/K^+ ATPase contributes to rapid restoration of neuronal membrane potential after rapid depolarization. The α subunits bind and transport Na^+ and K^+ and reduction in their activity result in different neurological diseases[15]. The heterogeneity of *ATP1A3* mutations results in the phenotypic variation observed. The role of the *ATP1A3* gene mutations is unclear. Genotype-phenotype correlations are not definite, but may exist.

The present case report is a rare case of *ATP1A3* gene mutation. It does not fit the RDP, AHC, CAPOS or D-DEMØ criteria, which means that it is either an atypical case of *ATP1A3* mutation or the remaining criteria have not yet been met. When comparing our patient's phenotype with RDP, differences include absence of dystonia or hyperreflexia and very early presentation of symptoms. Features shared with AHC include early onset of symptoms, global developmental delay and seizures at a later, however, time. Nonetheless, no episodes of alternating hemiplegia, dystonia, quadriplegia or autonomic dysfunction have been noted. The young age of the patient does not allow for comparison with CAPOS features. Also, when compared with D-DEMØ, similarities include encephalopathy with developmental delay, absence of hemiplegia and neonatal onset of symptoms. In contrast, dystonia and facial dysmorphism are absent, whereas cerebellar hypoplasia was also not identified on brain MRI. It should be noted

Table I. Blood test results on different days of life during hospitalisation.

Day 2									
WBC: 14.000	P: 63%, L: 27%, M:4%	Hct: 34.4%, Hb: 11 g/dl	PLT: 313000/µl	Glucose: 356 mg/dl	CRP: 0.3 mg/dl	Na: 137 mmol/l	K: 4.2 mmol/l	Ca: 6.6 mg/dl	P: 9.6 mg/dl
Mg: 1.8 mg/dl	Cl: 102 mEq/l	BUN: 20 mg/dl	Creat: 0.9 mg/dl	ALP: 169 U/l	Total protein: 4.4 gr/dl	Albumin: 3.1 g/dl	SGOT: 35 U/l	SGPT: 18 U/l	GGT: 162 U/l
CPK: 958 U/l	LDH: 481 U/l	Bilirubin: 5.9 mg/dl, Direct Bilirubin: 0.5 mg/dl	PT: 14.8 sec, aPTT: 135.6 sec, INR: 1.38, Fibrinogen: 212 mg/dl, D-Dimers: 1.89 mg/dl	SARS-CoV-2 PCR: negative	Urine tests: pH: 6, SG: 1020, WBC: 0-1, RBC: 3-5, ketones: +++				
Day 3									
Toxicology screen blood tests: negative.									
Brain ultrasound: normal.									
Abdominal ultrasound: normal.									
EEG: normal.									
CSF neurotransmitters: **Biogenic amines** 5 Hydroxy Indolacetic Acid (5HIAA): 188.00 nmol/L (428.00-1122.00) Homovanilic acid (HVA): 67.00 nmol/L (658.00-1434.00) 3 Orthomethyl Dopa (3OMD): 79.00 nmol/L (24.00-148.00) 5 Hydroxy Tryptophan (5OH Trp): 6.00 nmol/L (6.00-24.00) HVA/5HIAA ratio: 0.36 (0.76-1.67) **Pterines** Neopterin: 12.00 nmol/L (12.00-64.00) Biopterin: 22.00 nmol/L (22.00-70.00)									
Biochemical serum metabolites: Lactic acid: 2.50 mmol/L (fasting: 0.60-2.20) Pyruvate acid: 0.14 mmol/L (fasting: 0.04-0.14) 3 hydroxy butyric acid: 0.25 mmol/L (Fasting: 0.10-0.20) Aceto-acetic acid: 0.25 mmol/L (Fasting: 0.10-0.25) 3 hydroxy butyric acid/aceto-acetic acid: 1.00 (Fasting: <1) Total free lipid acids (FFA): 0.16 mmol/L (0.50-1.60) Total FFA/3 hydroxy Butyric: 0.64									
Day 4									
CSF: clear colour, WBC count: 13, WBC types: Neutrophils: 3, Lymphocytes: 6, Monocytes: 4, RBC count: 3, Protein: 7 mg/dl, Glucose: 56, Microbial examination: no organism. CSF culture: negative.									
Retinoscopy: normal.									
NH_4: 64 µmol/l (Normal values: 56-92)									
Day 5									
WBC: 11650	P: 27.9, L: 58.6, M:11.6%	Hct: 31%, Hb: 11.9 g/dl	PLT: 534000/µl	Glucose: 98 mg/dl	CRP: 0.01 mg/dl	Na: 111 mmol/l	K: 6 mmol/l	Ca: 6.6 mg/dl	P: 4 mg/dl
Mg: 1.5 mg/dl		BUN: 14 mg/dl	Creat: 0.3 mg/dl	ALP: 132 U/l	Total protein: 5.2 gr/dl	Albumin: 3.7 g/dl	SGOT: 20 U/l	SGPT: 12 U/l	GGT: 118 U/l
CPK: 369 U/l		Bilirubin: 9.25 mg/dl, Direct Bilirubin: 0.98 mg/dl							

Table II. Endocrine investigations during hospitalisation.

Day 6 of life	Day 10 of life	Day 17 of life
TSH: 5.1 mIU/L, FT4: 2.41 ng/dl	FSH: 5.3 mIU/ml	Aldosterone: 1000 pg/ml
PTH: 46.3 pg/ml	LH: 0.78 mIU/ml	Renin: 125 pg/ml
25-OH-VitD: 18.89 ng/ml	c-peptide: 1.7 ng/ml	Insulin: 2.6 μIU/ml
Aldosterone: 760 pg/ml	Testosterone: 54.39 ng/dl, DHEAS: 164.6 μg/dl	
Testosterone: 323.9 ng/dl, DHEAS: 485.5 μg/dl, Androstenedione: 9.2 ng/ml, 17-OH-Progesterone: 11.5 ng/ml		
Cortisol: 22.03 μg/dl		
ACTH: 10.4 pg/ml		
Progesterone: 4.86 ng/ml		
ADH: 9.1 pg/ml		

though that the MRI scan was performed at the neonatal age.

In addition, a common diagnosis, neonatal sepsis, was initially suspected due to the atypical clinical symptoms on presentation and the hypothesized stress-induced hyperglycaemia. However, during the course of the illness an infectious aetiology was considered unlikely given the negative blood and cerebral spinal fluid bacterial cultures, as well as the negative viral studies. Besides neonatal sepsis, the differential diagnosis was felt to include acute encephalopathy, endocrine disease, which was soon excluded by the clinical course and the endocrine test results, metabolic disorder, neurological or renal disease. Uncertainty about the diagnosis and the inability of the therapeutic team to establish a unifying diagnosis, led to genetic testing.

Conclusions

The present case report describes the diagnostic challenge posed by a rare genetic disorder and extends the already described phenotypic variation observed in individuals with *ATP1A3* gene mutations. The particularly early onset of the clinical symptoms, starting from the second day of life, adds to the rarity of the case. Furthermore, the co-existence of a variety of symptoms highlights the complexity of this case. More importantly, it also illustrates how difficult it may be to either determine whether a unifying diagnosis can explain the presenting symptoms or to distinguish which symptoms are associated with a specific entity and which may be caused by other factors that have a cumulative effect on the phenotype, such as iatrogenic complications. It also underlines the importance of considering genetic testing in the context of complex clinical scenarios, particularly when present from the neonatal age and when not all symptoms have developed, thus the phenotype is not yet typical of a specific diagnosis.

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Conflicts of Interest
The authors declare no conflicts of interest.

ORCID ID
Eirini Kostopoulou: 0000-0002-7051-7537.

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