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Case Report

Aminoacylase-1 Deficiency in a Lebanese Infant with a Novel Homozygous Variant

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Abstract

Aminoacylase 1 (ACY1) deficiency is a rare autosomal recessive inborn error of metabolism characterized by impaired hydrolysis of N-acetylated amino acids and a broad clinical spectrum, including developmental delay, seizures, and hypotonia. Fewer than 20 cases have been reported worldwide. Here we present the first reported case of ACY1 deficiency in a Lebanese infant born to consanguineous parents, highlighting the diagnostic challenges and phenotypic variability associated with this disorder. Whole exome sequencing (WES) identified a novel unreported homozygous variant in the *ACY1* gene, despite an otherwise normal biochemical screen. This case expands the clinical and genetic spectrum of ACY1 deficiency and underscores the importance of genetic testing in patients with unexplained neurodevelopmental delay.

Keywords: *ACY1 deficiency, Aminoacylase 1, Neurodevelopmental delay, Consanguinity, Whole exome sequencing, Lebanon.*

Introduction

With the growing advances in molecular genetics, rare inborn errors of metabolism are increasingly being identified, particularly in populations with high rates of consanguinity. Aminoacylase 1 (ACY1; EC 3.5.1.14) is the most prominent enzyme of the aminoacylase family, which is responsible for the hydrolysis of N-acetylated amino acids, a highly conserved process involved in protein metabolism [1].

ACY1 deficiency is an extremely rare autosomal recessive metabolic disorder caused by variants in the *ACY1* gene on chromosome 3p21, with fewer than 20 cases reported worldwide [2]. The clinical presentation is highly variable, ranging from intellectual disability, motor delay, and seizures to severe neurodevelopmental impairment, absent speech, growth delay, muscular hypotonia, and autistic features. Biochemically, affected individuals typically demonstrate increased urinary excretion of specific N-acetyl amino acids. Definitive diagnosis is established either by molecular genetic analysis or by measurement of enzyme activity.

Consanguinity is a well-recognized risk factor for autosomal recessive disorders, as it increases the likelihood of inheriting pathogenic variants from a common ancestor, thereby contributing to increased morbidity and mortality in affected offspring [3]. This is particularly relevant in the Arab world, where consanguineous marriages remain highly prevalent. In some countries, first-cousin marriages account for up to 25–30% of all unions, while in Lebanon the rate has been reported to reach approximately 35.5%.

Here, we report the first case of ACY1 deficiency in Lebanon in a female infant born to consanguineous parents, further expanding the clinical and genetic spectrum of this rare disorder.

Case Presentation

We report the case of a 5-month-old female infant from North Lebanon, referred for evaluation of neurodevelopmental delay and failure to thrive. She was born at term to consanguineous parents, from Northern Lebanon (figure 1), who were both asymptomatic, with one healthy sibling. There was no significant family history of neurological or metabolic disease.

Symptoms were first noted at 2 months of age, when the parents observed abnormal visual behavior, including poor fixation and inability to follow the light of shiny moving objects. By 4 months of age, the patient developed significant axial hypotonia and was unable to achieve adequate head control.

An ophthalmologic evaluation was performed due to suspected visual impairment; however, electroretinography (ERG) was normal. On physical examination, the patient exhibited poor interaction, severe axial hypotonia, and a head lag. The patient had a head circumference at the 50th percentile for her age. Cardiopulmonary examination was unremarkable, with no dysmorphic features or skin lesions. A mild hepatomegaly was noted.

Initial laboratory investigations were within normal ranges for CPK, lactate, pyruvate, ammonia, chromatography of amino acids in blood organic acids in urine and neonatal tandem mass screening .

Electroencephalography (EEG) demonstrated rare bilateral slow waves. Brain MRI and MR spectroscopy were unremarkable.

During follow-up, the patient developed seizures and was started on levetiracetam at a dose of 20 mg/kg/day. A muscle and nerve biopsy were performed.

Muscle biopsy of the right quadriceps revealed features consistent with mitochondrial myopathy, including decreased activity of succinate dehydrogenase and ATP synthase, along with increased lipid accumulation in myofibrils. Therefore a supportive metabolic therapy including carnitine and coenzyme Q10, biotin and riboflavin was initiated.

Despite treatment, the patient continued to exhibit poor weight gain, persistent hypotonia, tremors, and limited interaction.

Given the inconclusive metabolic workup, whole exome sequencing (WES) was performed. This revealed a homozygous variant in the *ACY1* gene (NM_000666.2 - c.839A>C (pAsp280Ala), consistent with a diagnosis of aminoacylase 1 deficiency. Parental testing confirmed heterozygosity in both parents, supporting autosomal recessive inheritance.

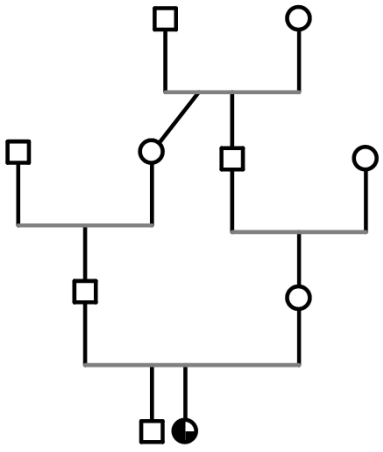

Figure 1

Discussion

Aminoacylase 1 deficiency is a rare autosomal recessive disorder caused by variants in *ACY1*, which encodes aminoacylase 1, a zinc-binding enzyme involved in the hydrolysis of N-acetylated amino acids. Since the first reported cases, ACY1 deficiency has shown a broad clinical spectrum, ranging from developmental delay, hypotonia, and seizures to milder neurocognitive phenotypes and even later-onset neurologic presentations [6,7].

In our case, the patient presented with early neurodevelopmental delay, axial hypotonia, seizures, and poor visual interaction, all of which fall within the neurologic spectrum reported in ACY1 deficiency. Genetic testing, specifically whole exome sequencing, identified a novel homozygous *ACY1* variant, and both parents were heterozygous carriers. This segregation pattern makes the variant the most likely cause of the presentation and highlights the importance of genetic testing in children with unexplained neurological diseases. [7,8]

Classically, *ACY1* variants are associated with increased urinary N-acetyl amino acids, including N-acetylalanine, N-acetylglycine, N-acetylmethionine, and N-acetylglutamic acid, since the deficiency prevents their normal breakdown. However, our case showed an unusual biochemical presentation, as the urinary organic acid analysis was normal. This further emphasizes the wide phenotypic and biochemical spectrum of the disease and indicates that a normal biochemical panel does not rule out the diagnosis. [6,7]

Another important finding in this case was the muscle biopsy, which showed reduced succinate dehydrogenase and ATP synthase activity, together with increased lipid accumulation in myofibrils, thus suggesting mitochondrial dysfunction. However, such findings are not restricted to primary mitochondrial disease and may also be seen in secondary mitochondrial dysfunction. Therefore, these abnormalities may represent a secondary consequence of the underlying disorder rather than a separate primary mitochondrial disease, and this is important in order to avoid overestimating the mitochondrial component of the clinical picture [9], while keeping in mind the importance of managing secondary mitochondrial dysfunction in order to reduce the severity of the symptoms.

This variant supports the wide range of clinical presentations that may occur in ACY1 deficiency, from severe developmental delay and autism to mild intellectual disability and even adult-onset movement disorders. Reports have also described autistic behavior and variable severity among affected siblings, which further shows how broad the neurologic phenotype can be. [10,11,12,13]

In our case, the patient presented in infancy with developmental delay with a novel homozygous p.Asp280Ala variant, a normal routine biochemical testing, and signs of mitochondrial dysfunction on muscle biopsy.

To our knowledge, this may be the first reported Lebanese infant with an *ACY1*-related phenotype associated with a novel homozygous *ACY1* c.839A>C (p.Asp280Ala) variant.

Therefore, this case expands the known clinical and genetic spectrum of *ACY1*-related disease by describing a Lebanese infant with a compatible neurologic phenotype, atypical urine biochemical testing, and muscle-biopsy evidence of mitochondrial dysfunction in association with a novel homozygous *ACY1* variant. It also highlights the importance of whole exome sequencing in infants with unexplained neurodevelopmental delay when first-line metabolic investigations are unrevealing. [6,9,12,15]

Conclusion

We report the first Lebanese case of ACY1 deficiency in a female infant presenting with neurodevelopmental delay, seizures, and hypotonia. This case highlights the diagnostic challenges associated with this rare disorder, particularly in the absence of typical biochemical findings. Whole exome sequencing proved essential in establishing the diagnosis.

Our findings emphasize the importance of considering rare metabolic disorders in infants with unexplained neurological symptoms, especially in populations with high rates of consanguinity. Genetic counseling is strongly recommended for affected families.

Conflict of Interest

The authors declare no conflict of interest.

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