MEGDEL Syndrome: Two New Cases and Diagnostic Value of 3-Methylglutaconic Aciduria

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Introduction

3-Methylglutaconic aciduria (3-MGA-uria) represents a heterogeneous group of inborn errors of metabolism, whose common biochemical feature is urinary excretion of 3-methylglutaconic and 3-methylglutaric acids. Consistent 3-MGA-uria is also a marker for mitochondrial dysfunction, and the hallmark of a growing group of inborn errors of metabolism (IEM) due to defective phospholipid remodeling or mitochondrial membrane-associated disorders (mutations in TAZ, SERAC1, OPA3, CLPB, DNAJC19, TMEM70, TIMM50) (Kovacs-Nagy, Morin et al. 2018). MEGDEL Syndrome (3-MGA-uria, deafness, encephalopathy and Leigh-like syndrome) is a rare specific mitochondrial disorder due to mutations in SERAC1 gene (Wortmann, Rodenburg et al. 2006). The SERAC1 gene encodes for a phosphatidylglycerol remodeler, essential for mitochondrial functions and intracellular cholesterol trafficking (Finsterer, Scorza et al. 2020). Since the first description of MEGDEL syndrome in 2006, at least 102 patients have been reported (Finsterer, Scorza et al. 2020).

Cases report

We herein report two cases (twin identical brothers), who presented with sensorineural hearing loss at 6-month-old (passed newborn hearing screening). Both developed moderate generalized hypotonia and showed signs of delay in language and motor development. Laboratory abnormalities include mild lactate acidemia, 2.8 (0.7-2.2 mmol/L) and elevated liver enzyme: AST 93 (20-60 unit/L), ALT 57 (12-45 unit/L). Urine organic acids by gas chromatography-mass spectra (GC/MS) showed markedly elevation of 3-methylglutaconic acid and 3-methylglutaric acid (Fig1). Brain MRI showed symmetric restricted diffusion involving the globi pallidi, cerebral peduncles and hippocampi and virtually identical finding in the patient's twin, a genetic etiology related to Leigh’s disease was suggested (Fig2). Mitochondrial encephalopathy/Leigh Syndrome Nuclear gene panel/Sequencing and deletion/duplication analysis of 134 genes demonstrated two heterozygous pathogenic variants in the SERAC1 gene: C.227_228dupAT (p.V77MfsX7) and C.916C>T(p.R306X), confirming MEGDEL diagnosis when the twins were 21-month-old. Both are receiving physical therapy and are making slow progress.
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Discussion

We report two patients with MEGDEL syndrome presenting with sensorineural hearing loss, hypotonia, delayed language and motor development, lactic acidemia with Leigh disease in brain MRI. The phenotype points toward the direction of mitochondrial diseases. 3-MGA-uria and molecular study confirmed the diagnosis of MEGDEL syndrome. These two cases highlight the diagnostic challenge clinicians can face in the diagnosis of a heterogeneous group of mitochondrial diseases, such as MEGDEL syndrome in this case.

3-MGA-uria can be primary or secondary. Primary 3-MGA-uria (type I) refers to the well-defined 3-methylglutaconyl-CoA hydratase deficiency due to mutations in AUH gene. Secondary 3-MGA-uria refer to disorders caused by different genes related to mitochondrial dysfunction, such as Barth syndrome (TAZ), type II, Costeff syndrome (OPA3) type III, MEGDEL syndrome (SERAC1) type IV, DCMA syndrome (DNAJC19) type V, TMEM70 defect (TMEM70) type IV, and not otherwise specified (NOS) 3-MGA-uria (Wortmann, Duran et al. 2013). Even though the mechanism of secondary 3-MGA-uria still needs to be elucidated but was thought to be related to cholesterol metabolism. The fast-increasing numbers of genes (CLPB, HTRA2/Omi, ECHS1, TIMM50, LYRM4, etc.) associated with secondary 3-MGA-uria make this noninvasive and inexpensive testing of urinary organic acid analysis very valuable in assistance with diagnosis of mitochondrial diseases. It can guide further genetic testing in children with suggestive clinical findings associate with mitochondrial diseases.

Conclusion

We propose patients with 3-MGA-uria should have medically necessary further investigation, such as molecular testing to distinguish the known types including Type I (AUH) and other disorders, such as mitochondrial diseases that cause secondary 3-MGA-uria. Whole Exome/genome sequencing is definitely a very powerful tool for the diagnosis of this clinically and genetically heterogeneous group of disorders.

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*Fig 1. Chromatogram of urinary organic acids analysis by GC/MS*

IS (Internal Standard): 4-Chlorobenzoic acid
ES (External Standard): Tetracosane
1. 3-hydroxyisovaleric acid
2. 3-methylglutaric acid
3. 3-methylglutaconic acid #1
4. 3-methylglutaconic acid #2
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Fig. 2 Brain MRI showing T2 hyperintensities (A-D) and bilateral symmetric restricted diffusion (A,B) associated with MEGDEL. Axial T2-weighted trace: A) Cerebral peduncles, B) Globi pallidi. Coronal fast spin-echo inversion recovery T2-weighted: C) Cerebral peduncles, D) Globi pallidi. Arrows indicate respective hyperintensities. Not included were slight T2 intensities seen in hippocampi.
References

