Coincidence of 3-methylglutaconic aciduria and duplication 5q – a case report and literature review

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3-methylglutaconic aciduria includes a heterogeneous group of inborn errors of metabolism. The disease may have various clinical presentations, as can duplication 5q. We present the case of a 13-year-old boy with 3-methylglutaconic aciduria and duplication 5q. The main symptoms included myopathy, weakness, spastic paresis intensified mostly in the lower limbs, and intellectual disability. Additional studies showed elevated levels of 3-methylglutaconic acid in urine and ammonia in plasma. A duplication in region 5q23.3q31.1 was found in array-based comparative genomic hybridization. Next-generation sequencing did not reveal any pathological mutation. On the basis of the clinical picture and the results of biochemical and genetic tests 3-methylglutaconic aciduria type IV with duplication 5q was diagnosed.

Key words: duplication, 3-methylglutaconic aciduria, myopathy, intellectual disability

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INTRODUCTION

3-methylglutaconic aciduria is a heterogeneous group of diseases whose common biochemical feature is the excretion of 3-methylglutaconic acid. Clinical features are varied and may include, among others, leukoencephalopathy, cardiomyopathy, failure to thrive, neutropenia, spastic paresis, hyperreflexia, and intellectual disability. Currently, 9 types of disease are distinguished, most of them are inherited in an autosomal recessive way, while type II (Barth syndrome) is an X-linked recessive disease (Kawalec et al., 2018; OMIM, PS250950, 2020).

Familial cases of duplication 5q were associated with intellectual disability, microcephaly, micrognathia, dysmorphic features, brachyactyly and growth retardation (Martin et al., 1985; Arens et al., 2004). The aim of the study was to draw attention to a rare metabolic disease and the possibility of coexistence of a chromosome abnormality, as well as to consider its impact on the clinical picture.

CASE PRESENTATION

A 13-year-old boy from first pregnancy-first labor was born on time (hbd 40) through the natural passages with a birth weight of 3750 g and 10 points according to the Apgar scale. The mother felt the fetal movement poorly during pregnancy. The patient’s motor development was normal, while the speech development was delayed - the first words after 3 years of age. Since the boy was 6 years old, a gait deterioration, impaired manual function, and school difficulties have been observed. The patient still experiences significant generalized weakness, especially after physical education classes, and muscle pain in the shank, thigh and pelvic girdle. There are café au lait patches on the skin (Fig. 1). Neurologic examination revealed predominant spastic paraparesis and contractures in the knee and ankle joints. Mild intellectual disability was also diagnosed, the patient attends inclusive school. In family history, there were no metabolic diseases, but the proband’s stepbrother also has café au lait patches.

Figure 1. Café au lait patches on the patient’s abdomen and back.

In connection with the history and clinical picture, diagnostics for metabolic diseases was carried out. In the urine organic acid profile determined by the gas chromatography-mass spectrometry (GC/MS) method, borderline but recurrent elevated levels of 3-methylglutaconic acid were found (20 mmol/mol creatinine, norm range <20 mmol/mol creatinine). Attention was also drawn to slightly elevated blood ammonia (90–120 with a standard of 20–80 μg/dl). The results of other laboratory tests: plasma amino acids concentration, blood lactic acid level, biotinidase and creatine kinase activity, as well as the pattern of transferrin isoforms, remained within the reference range.

Magnetic resonance imaging (MRI) of the central nervous system and the thoracic segment of the spine showed no pathology, nor did EEG. In EMG, myogenic
signals were observed. The somatosensory evoked potentials (SEP) study of the tibial nerves revealed abnormal signals of the right tibial nerve.

Due to suspected myopathy, a biopsy of the right biceps brachii was performed. Microscopic analysis revealed discrete, non-characteristic lesions in the form of slight connective tissue hypertrophy in perimysium and atrophy of type 2 fibers (enzymatic staining). Fragile X syndrome (FXS) was excluded. Microarray-based Comparative Genomic Hybridization (aCGH) with probes of definition 8x60k, SurePrint G3 CGH ISCA v2 (Agilent) was performed. 6.56-Mbp long duplication of the long arm of chromosome 5 was detected – arr[GRCh37/hg19] 5q23.3q31.1(129439472_135995612)x3. The above result was confirmed using fluorescence in situ hybridization (FISH).

WES study by next-generation sequencing (on the Illumina HiSeq 1500 platform) revealed no mutation in any of the known genes associated with 3-methylglutaconic aciduria. Despite the clinical picture that differs from the previous reports, it seems appropriate to classify the disease as 3-MGA type IV.

Increased excretion of 3-methylglutaconic acid may be a part of other metabolic and non-metabolic diseases. Wortmann and others (Wortmann et al., 2013) analyzed 977 cases of 3-methylglutaconic aciduria. Out of this group, 23 patients (8%) had 3-methylglutaconic aciduria as a differentiating feature, 61 patients (22%) had a typical metabolic disease (e.g., defects of fatty acids oxidation or urea cycle disorders), 43 patients (16%) had a different disease (hematologic, neuromuscular or a genetic syndrome), 49 patients (18%) had a mitochondrial disease, 10 patients (4%) had transient aciduria during hypoglycemia episodes, while in 41 patients (15%) no cause was found (Wortmann et al., 2013). Single reports and case series are also available in the literature showing the co-occurrence of 3-methylglutaconic aciduria with other diseases (Kelley & Kratz, 1995; Sato et al., 2015; Rokicki et al., 2017; Sağ et al., 2019).

Increased production and excretion of 3-methylglutaconic acid may also occur in sterol and isoprenoid biosynthesis disorders. This is due to the increased activity of the mevalonate shunt, which combines cholesterol biosynthesis with the leucine catabolism pathway (Fig. 2). Kelley and Kratz analyzed a group of 35 patients with Smith-Lemli-Opitz syndrome and demonstrated a weak inverse correlation between the reduced plasma cholesterol level and increased concentration of 7-dehydrocholesterol and 3-methylglutaconic acid (Kelley & Kratz, 1995).

According to the literature, despite numerous coincidences of 3-methylglutaconic aciduria with a number of different disease entities, the coexistence of duplication 5q has not been described yet. Cases of duplication within the long arm of chromosome 5 have been reported in the medical press since

**DISCUSSION**

3-methylglutaconic aciduria (3-MGA) is a heterogeneous group of inborn errors of metabolism. 3-methylglutaconic acid is formed together with 3-methylglutaric acid and 3-methylglutarylcarnitine from 3-methylglutaryl-CoA in the pathway of leucine catabolism (Fig. 2) (Wortmann et al., 2012). Currently, 9 types of the disease are known, of which 8 (I–III and V–IX) have a determined genetic cause. 3-methylglutaconic aciduria type IV includes a heterogeneous group of diseases, with not yet defined cause and a variable clinical picture, usually including psychomotor development delay, hypotonia or hypertonia, seizures, abnormalities within the heart and central nervous system. The disease usually has a progressive course and leads to death in infancy (Jareño et al., 2007; Wortmann et al., 2012; OMIM, PS250950, 2020). The dominant symptoms in the patient were myopathy, weakness, and spastic paraparesis. The next-generation sequencing did not reveal mutations in known genes responsible for the occurrence of 3-methylglutaconic aciduria. Despite the clinical picture that differs from the previous reports, it seems appropriate to classify the disease as 3-MGA type IV.
the 1980s. Reports concerning the same rearranged region as in our patient included various clinical features: microcephaly, micrognathia, strabismus, congenital heart defects, mental retardation, narrower upslanting palpebral fissures, dysmorphic ears, falling corners of the mouth, high-arched palate, long philtrum, hypoplasia of the corpus callosum, periventricular leucomalacia, prominent occiput, hypertelorism, intrauterine growth retardation, cryptorchidism, and club foot (Martin et al., 1985; Rauen et al., 2001; Arens et al., 2004; Giardino et al., 2004; Dutta et al., 2013).

The occurrence of duplication in the offspring is usually associated with inheriting it from the parent carriers or appears de novo. In duplication 5q cases, it is difficult to distinguish a specific clinical syndrome due to the frequent presence of microdeletions in other chromosomes as a result of incorrect chromosome segregation in the co-occurrence of balanced translocation (Giardino et al., 2004). In the reported case, myopathy, weakness after physical effort and spastic paraparesis were the main features. Due to the correct result of the WES test, duplication at the loci 5q23.3q31.1 probably had a key influence on foregoing abnormalities. The proband's parents did not present features that indicate microduplication syndrome, whereas the origin of the change had not been determined yet.

The duplicated region 5q23.3q31.1 of 6.56 Mb contains 72 genes (OMIM, GeneMap, 2020). Among them, there are 4 genes: HENT1, LYRM7, UGCRQ, PPP2CA, that are associated with neurological and mitochondrial diseases, respectively; neuromyotonia and axonal neuropathy (OMIM, #137200, 2017), mitochondrial complex III deficiency, nuclear type 8 (OMIM, #615838, 2018) and nuclear type 4 (OMIM, #615159, 2017), and neurodevelopmental disorder and language delay with or without structural brain abnormalities (OMIM, #618354, 2019). These syndromes are characterized by, among others, muscle weakness, intellectual disability, hypotonia, hyponatraemia, hyperammonemia, which partly correspond to the clinical picture of the described patient.

An additional symptom that draws attention is the presence of small (about 1 cm in diameter) café au lait patches (CAL) on the boy’s abdomen and back (a total of 4). Between 10 and 20% of adults have at least one CAL patch. These skin changes are associated with several diseases, primarily neurofibromatosis type 1, in which neurofibromas, Lisch nodules, and renal artery stenosis also appear. Another disease characterized by CAL patches is McCune-Albright syndrome, in which skin lesions are usually extensive and have irregular borders. In addition, café au lait patches may also appear in Legius syndrome, Silver-Russell syndrome, neurofibromatosis type 2, and ring chromosomes syndromes (Rear- don, 2016; Firth & Hurst, 2017). The lack of symptoms suggesting the above-mentioned diseases and the correct WES result rather indicate the sporadic nature of café au lait patches in our patient.

CONCLUSIONS

3-methylglutaconic aciduria may be a separate disease entity from the group of inborn errors of metabolism, as well as co-occur with other diseases. In the presented case, the dominant symptoms, i.e. myopathy, weakness, spastic paraparesis, and mild intellectual disability probably result from relatively large duplication within the long arm of chromosome 5. The correct result of exome sequencing indicated the qualification of 3-methylglutaconic aciduria to a broad group of entities that type IV of this disease covers. The aCGH study may reveal a microdeletion or microduplication that may affect the patient’s phenotype. Therefore, it seems reasonable to conduct this study in similar cases of an unclear clinical picture, even if the biochemical tests indicate a specific metabolic disease. In cases of undiagnosed developmental delay or intellectual disability and dysmorphic features, it is advisable to prosecute diagnostics recommended by the American Society of Human Genetics (Miller et al., 2010).

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