ACTA ABP BIOCHIMICA POLONICA

Vol. 67, No 2/2020
263–266
https://doi.org/10.18388/abp.2020_5355

Regular paper

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

Paweł Zapolnik[1]✉, Jolanta Sykut-Cegielska[2] and Antoni Pyrkosz[3]

[1]Students' Scientific Association of Clinical Genetics, Department of Clinical Genetics, Medical College, University of Rzeszów, Rzeszów, Poland; [2]Department of Inborn Errors of Metabolism and Paediatrics, Institute of Mother and Child, Warsaw, Poland; [3]Department of Clinical Genetics, Medical College, University of Rzeszów, Rzeszów, Poland

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

Received: 24 April, 2020; revised: 29 April, 2020; accepted: 11 May, 2020; available on-line: 08 June, 2020

✉e-mail: pawel.zapolnik@onet.pl

Abbreviations: aCGH, microarray-based Comparative Genomic Hybridization; GC/MS, gas chromatography-mass spectrometry; 3-MGA, 3-methylglutaconic aciduria; MRI, magnetic resonance imaging; FISH, fluorescence *in situ* hybridization; FXS, fragile X syndrome; SEP, somatosensory evoked potentials

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, brachydactyly 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.

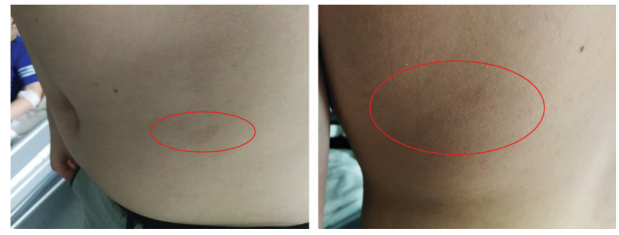

Figure 1. Café au lait patches on the patient's abdomen and back.

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

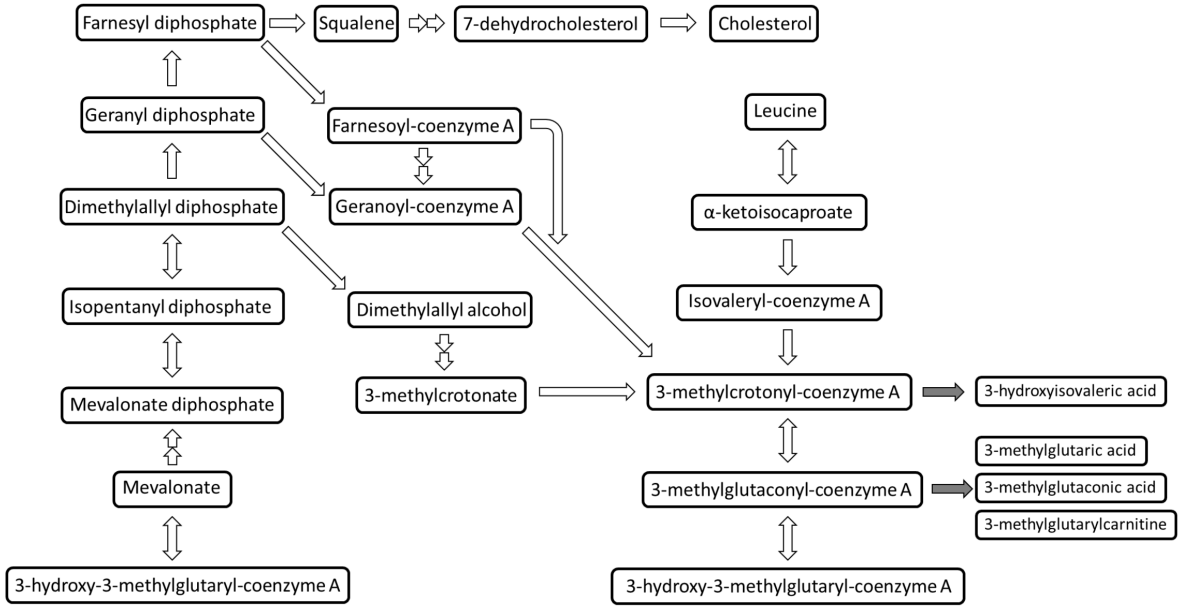

Figure 2. Diagram presenting the linkage between the sterol biosynthesis and the pathway of leucine catabolism.

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**.**

On the basis of the clinical picture and the results of biochemical and genetic tests 3-methylglutaconic aciduria type IV (i.e. of undetermined genetic cause) with myopathy and spastic paraparesis was diagnosed.

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-methylglutaconyl-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.

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

the 1980s. Reports concerning the same rearranged region as in our patient included various clinical features: microcephaly, micrognathia, strabismus, congenital heart defects, mental retardation, narrowed 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 Mbp contains 72 genes (OMIM, GeneMap, 2020). Among them, there are 4 genes: *HINT1*, *LYRM7*, *UQCRQ*, *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, hyperreflexia, 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 (Reardon, 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).

Acknowledgments

We would like to thank professor Artur Mazur for help in diagnosing the patient and preparing this paper.

REFERENCES

Arens YH, Engelen JJ, Govaerts LC, van Ravenswaay CM, Loneus WH, van Lent-Albrechts JC, van der Blij-Philipsen M, Hamers AJ, Schrander-Stumpel CT (2004) Familial insertion (3;5)(q25.3;q22.1q31.3) with deletion or duplication of chromosome region 5q22.1-5q31.3 in ten unbalanced carriers. *Am J Med Genet A.* **130A**: 128–133. https://doi.org/10.1002/ajmg.a.20568

Dutta MK, Gundgurthi A, Garg MK, Pakhetr R (2013) Cryptorchidism due to chromosome 5q inversion duplication. *J Assoc Physicians India* **61**: 925–927.

Firth HV, Hurst JA (2017) *Oxford Desk Reference Clinical Genetics & Genomics*. Oxford: pp. 278–279. Oxford University Press.

Giardino D, Finelli P, Amico FP, Gottardi G, Civa R, Corona G, Nocera G, Larizza L (2004) Unbalanced segregation of a complex fourbreak 5q23-31 insertion in the 5p13 band in a malformed child. *Eur J Hum Genet* **12**: 455–459. https://doi.org/10.1038/sj.ejhg.5201150

Jareño NM, Fernández-Mayoralas DM, Silvestre CP, Cortés BM, Pérez MU, Campos-Castelló J (2007) 3-methylglutaconic aciduria type 4 manifesting as Leigh syndrome in 2 siblings. *J Child Neurol* **22**: 218–221. https://doi.org/10.1177/0883073807300300

Kawalec W, Grenda R, Kulus M (2018) *Pediatria I*. Warszawa: p. 265. PZWL Wydawnictwo Lekarskie.

Kelley RI, Kratz L (1995) 3-methylglutaconic acidemia in Smith-Lemli-Opitz syndrome. *Pediatr Res* **37**: 671–674. https://doi.org/10.1203/00006450-199505000-00020

Martin NJ, Cartwright DW, Harvey PJ (1985) Duplication 5q(5q22---5q33): from an intrachromosomal insertion. *Am J Med Genet* **20**: 57–62. https://doi.org/10.1002/ajmg.1320200109

Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, Church DM, Crolla JA, Eichler EE, Epstein CJ, Faucett WA, Feuk L, Friedman JM, Hamosh A, Jackson L, Kaminsky EB, Kok K, Krantz ID, Kuhn RM, Lee C, Ostell JM, Rosenberg C, Scherer SW, Spinner NB, Stavropoulos DJ, Tepperberg JH, Thorland EC, Vermeesch JR, Waggoner DJ, Watson MS, Martin CL, Ledbetter DH (2010) Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet* **86**: 749–764. https://doi.org/10.1016/j.ajhg.2010.04.006

Online Mendelian Inheritance in Man. https://www.omim.org/phenotypicSeries/PS250950 Access 19th April 2020.

Online Mendelian Inheritance in Man. https://www.omim.org/geneMap/5 Access 20th March 2020

Online Mendelian Inheritance in Man. https://www.omim.org/entry/137200 Last edited 05/01/2017; Access 19th April 2020

Online Mendelian Inheritance in Man. https://www.omim.org/entry/615838 Last edited 11/27/2018; Access 19th April 2020

Online Mendelian Inheritance in Man. https://www.omim.org/entry/615159 Last edited 08/16/2017; Access 19th April 2020

Online Mendelian Inheritance in Man. https://www.omim.org/entry/618354 Last edited 03/18/2019; Access 19th April 2020

Rauen KA, Bitts SM, Li L, Golabi M, Cotter PD (2001) Tandem duplication mosaicism: characterization of a mosaic dup(5q) and review. *Clin Genet* **60**: 366–370. https://doi.org/10.1034/j.1399-0004.2001.600508.x

Reardon W (2016) *The Bedside Dysmorphologist*. New York, NY: pp. 334–336. Oxford University Press.

Rokicki D, Pajdowska M, Trubicka J, Thong MK, Ciara E, Piekutowska-Abramczuk D, Pronicki M, Sikora R, Haidar R, Oltarzewski M, Jabłońska E, Muthukumarasamy P, Sthaneswar P, Gan CS, Krajewska-Walasek M, Carrozzo R, Verrigni D, Semeraro M, Rizzo C, Taurisano R, Alhaddad B, Kovacs-Nagy R, Haack TB, Dionisi-Vici C, Pronicka E, Wortmann SB (2017) 3-Methylglutaconic aciduria, a frequent but underrecognized finding in carbamoyl phosphate

synthetase I deficiency. *Clin Chim Acta* **471**: 95–100. https://doi.org/10.1016/j.cca.2017.05.023

Sağ E, Kamaşak T, Kaya G, Çakır M (2019) A rare clinical association: Barth syndrome and cystic fibrosis. *Turk J Pediatr* **61**: 134–138. https://doi.org/10.24953/turkjped.2019.01.023.

Sato T, Muroya K, Hanakawa J, Iwano R, Asakura Y, Tanaka Y, Murayama K, Ohtake A, Hasegawa T, Adachi M (2015) Clinical manifestations and enzymatic activities of mitochondrial respiratory chain complexes in Pearson marrow-pancreas syndrome with 3-methylglutaconic aciduria: a case report and literature review. *Eur J Pediatr* **174**: 1593–1602. https://doi.org/10.1007/s00431-015-2576-7

Wortmann SB, Kluijtmans LA, Engelke UF, Wevers RA, Morava E (2012) The 3-methylglutaconic acidurias: what's new? *J Inherit Metab Dis* **35**: 13–22. https://doi.org/10.1007/s10545-010-9210-7

Wortmann SB, Kluijtmans LA, Rodenburg RJ, Sass JO, Nouws J, van Kaauwen EP, Kleefstra T, Tranebjaerg L, de Vries MC, Isohanni P, Walter K, Alkuraya FS, Smuts I, Reinecke CJ, van der Westhuizen FH, Thorburn D, Smeitink JA, Morava E, Wevers RA (2013) 3-Methylglutaconic aciduria – lessons from 50 genes and 977 patients. *J Inherit Metab Dis* **36**: 913–921. https://doi.org/10.1007/s10545-012-9579-6