Maradin, M., Fumić, K., Hansikova, H., Tesarova, M., Wenchich, L., Dorner, S., Sarnavka, V., Zeman, J., Barić, I. (2006) *Fumaric aciduria: Mild phenotype in a 8-year-old girl with novel mutations.* Journal of Inherited Metabolic Disease, 29 (5). 683.

http://www.springerlink.com/content/n8208g07j7555255/
The original publication is available at www.springelink.com

FUMARIC ACIDURIA: MILD PHENOTYPE IN A 8-YEAR-OLD GIRL WITH NOVEL MUTATIONS

M. Maradin[1], K. Fumić[1], H. Hansikova[2], M. Tesarova[2], L. Wenchich[2], S. Dorner[3], V. Sarnavka[3], J. Zeman[2], I. Barić[3*]

[1]Clinical Institute of Laboratory Diagnosis and [3]Department of Paediatrics, University Hospital Center Zagreb, Croatia; [2]Department of Pediatrics and Centre of Applied Genomics, Charles University, Prague, Czech Republic

**Send all correspondence to:*

Ivo Barić, MD, PhD,
Department of Pediatrics,
University Hospital Center,
Kišpatićeva 12, Rebro,
10000 Zagreb, Croatia.
Tel: +385-1-242-1824 Fax: +385-1-242-1894
E-mail: ibaric@kbc-zagreb.hr

Word counts:
Text: 707 (including summary)
Abstract: 250

Number of figures and tables: 0

Contribution of individual authors:

M. Maradin- biochemical analyses, drafting the article
K. Fumić- biochemical analyses, critical revision of the manuscript
H. Hansikova- laboratory analyses, critical revision of the mansucript
M. Tesarova- laboratory analyses, critical revision of the mansucript
L. Wenchich- laboratory analyses, critical revision of the mansucript
S. Dorner- analysis of clinical data, drafting the article, literature search
V. Sarnavka- managing the patient, critical revision of manuscript
J. Zeman- organization of laboratory studies, interpretation of the data, critical revision of the mansucript
I. Barić- managing the patient, design and critical revision of the manuscript

Guarantor- Ivo Barić

All authors declare that the answer to all questions on the JIMD competing interest form are "No", and therefore they have nothing to declare.

Details of funding: This research was supported by grants 0108016 (Republic of Croatia) and MSM 002160806 (Czech Republic).
All studies related to this work were independent from the sponsors.

No ethics approval was required.

There is no personal information about the patient in the manuscript.

ABSTRACT

Fumaric aciduria is a rare, autosomal recessive disorder caused by deficient acitivity of fumarate hydratase (FH). Common clinical features are hypotonia, failure to thrive, severe psychomotor retardation and seizures. Facial dysmorphism and brain malformations are frequent. Recently, some FH gene mutations have been associated with inherited cutaneous and uterine leiomyomas and papillary renal cell cancer. Our patient had a relatively mild phenotype, previously not reported genotype and familiar tumor predisposition. Mother and grandmother had uterine myomas. Paternal grandfather and his two brothers died from lung and laryngeal cancers. The pregnancy was complicated by bleeding and intrauterine growth retardation. Delivery was after 35 weeks, with normal Apgar score. The girl was hypotonic since birth. At age 2 months parents noticed short apnoic crises. She could sit at age 1.5 years, walk with assistance at 4 years. At age 8 years highly increased excretion of fumaric acid was found twice (217 and 445 mmol/mol creatinine). Shortly before that the girl started to have leg and arm spasms. *Grand mal* seizures ocurred twice. Facial dysmorphism included depressed nasal bridge, anteverted ears, hypertelorism and microcephaly. Speech was limited to few disyllables. She was atactic with spastic paraparesis. Brain MRI showed slight ventriculomegaly, white matter atrophy and hypoplasia of corpus callosum. Activity of FH in fibroblasts was 1.9 nmol/min/mg protein (controls 40-80). FH gene analysis revealed the maternally derived c. 1029_1031delAGT mutation, resulting in Val deletion and substitution of Gln into His, and paternally derived c. 976C>T mutation, resulting in substitution of Pro into Ser.

SUMMARY

Fumaric aciduria is a very rare disorder, with variable neurological symptomatology and mutations in the corresponding gene recently associated with tumorogenesis. We report a patient with mild phenotype and two novel mutations, at least one being related to familial tumors.

KEYWORDS

fumaric aciduria; mutations; genotype-phenotype correlation; tumor predisposition; uterine leiomyomas

RUNNING HEAD

mild fumaric aciduria with novel mutations

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OMIM catalogue number 606812, 136850
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Fumaric aciduria (McKusick 136850) is a rare, autosomal recessive disorder due to deficient acitivity of a Krebs cycle enzyme fumarate hydratase (FH). The most common clinical features are hypotonia, failure to thrive, severe psychomotor retardation and seizures. Facial dysmorphism and brain malformations are frequent (Kerrigan JF et al 2000). Twelve autosomal recessive mutations in the FH gene associated with FH deficiency have been reported so far. No genotype-phenotype correlation has been established. It has been shown recently that some of the germline mutations in the FH gene are associated with inherited cutaneous and uterine leiomyomas and papillary renal cell cancer (Tomlinson et al 2002). We report a patient with a relatively mild phenotype and two new mutations which could be associated with tumor development.

Patient is the only child of unrelated parents. Pregancy was complicated by bleeding and intrauterine growth retardation. Delivery was spontaneous after 35 weeks, with normal Apgar score. Birth weight 2200 g, length 45 cm, head circumference 31 cm. The girl was hypotonic since birth. At age 2 months parents noticed short apnoic crises. At age 6 months psychomotor delay became evident. Brain ultrasound revealed normotensive ventriculomegaly. She could sit at age 1.5 years, walk with assistance at 4 years. At age 8 years she started to have leg and arm spasms induced by various stimuli. Dysmorphic features included microcephaly, depressed nasal bridge, anteverted ears and hypertelorism. Speech was limited to few disyllables. She was atactic with spastic paraparesis and twice had *grand mal* type seizures. Brain MRI showed slight ventriculomegaly, white matter atrophy and hypoplasia of corpus callosum. Echocardiography revealed mitral valve prolapse with low grade regurgitation. Mother and maternal grandmother underwent surgery for uterine myomas. Paternal grandfather and his two brothers died from cancers (two lung cancers and one laringeal).

Routine biochemistry, plasma amino acids, blood and CSF lactate were normal. Urinary excretion of fumaric acid was high - 217 and 415 mmol/mol creatinine, respectively (normal <3.5). Activity of fumarate hydratase in fibroblasts was 1.9 nmol/min/mg protein (control: 40-80). Western blot analysis revealed severely decreased protein amount of FH. Analysis of FH gene revealed two mutations, both located in the highly conserved regions. The maternally derived one was the c.1029_1031delAGT mutation resulting in Val344del and Gln343His substitution (Q343H), while the paternally derived was the c.976C>T mutation resulting in Pro326Ser substitution. None of the two mutations could be detected in 124 Czech and 104 Croatian control chromosomes.

Fumaric aciduria is a very rare disorder with, to our knowledge, 32 patients from 23 families reported. The majority of patients from early reports had relatively severe clinical presentation with cerebral dysgenesis, almost absent psychomotoric development and death in early infancy. This mild case indicates that fumaric aciduria should be included in differential diagnosis of unexplained ataxia, delayed speech and relatively mild neurological impairment.

Our patient is a compound heterozygote for two novel mutations. Although, the precise influence of these novel mutations on loss of enzyme activity has to be explained in the future, it seems that they could be associated with relatively mild phenotype.

Another interesting aspect of FH gene mutations is related to the recent observations that FH acts as a tumor supressor and germline heterozygous mutations are associated with hereditary predisposition to papillary renal-cell carcinoma and leiomyomatosis. There was impression that these mutations tend to occur in 5'-end of the gene, whereas the FH deficiency mutations tend to appear more in the 3'-end. Some mutations have been associated with both tumorogenesis and diminished FH activity, for instance the R190H mutation. Since both mother and grandmother of our patient had uterine leiomyomas, the maternally derived mutatation in our case seems to be associated with both FH deficiency and tumor predisposition. Based on father's family history it is possible that the paternally derived mutation is associated with tumor development, as well. However, more data from family history and additional family testing would be necessary for more accurate conclusions. Unfortunately, so far, tissue from family members other than the patient and her parents is not available.

Supported by grants 0108016 (Republic of Croatia) and MSM 002160806 (Czech Republic).

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