Molecular Genetics and Metabolism Reports 12 (2017) 99–102

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Short Communication

A compound heterozygote case of isolated sulfite oxidase deficiency

Daniel Brumaru[a,*], Eric Guerin[a], Anne-Claire Voegeli[a], Didier Eyer[b], Michel Maitre[a]

[a] Hôpitaux Universitaires de Strasbourg, Laboratoire de Biochimie et Biologie Moléculaire, 67000 Strasbourg, France
[b] Hôpitaux Universitaires de Strasbourg, Service de Pédiatrie 3, 67000 Strasbourg, France

ARTICLE INFO

Keywords:
Compound heterozygote
Point mutation
Missense mutation
Transition
Transversion
Fibroblasts
Sulfite oxidase activity

ABSTRACT

We report an isolated sulfite oxidase deficiency in the first child boy of a non-consanguineous Caucasian family. He's a compound heterozygote for the sulfite oxidase gene, presenting low cystine, undetectable homocysteine and normal uric acid blood concentrations and undetectable sulfite oxidase activity in his cultured fibroblasts. Both mutations are not reported yet. The clinical presentation was typical and severe, with generalized status epilepticus and premature death.

1. Case report

A term infant boy was born to a primipara and primigesta mother from France and a father of Moroccan origin. No significant familial antecedents were reported.

A caesarean was performed at 37 weeks and 2 days because of non-progression of delivery and abnormalities of foetal heart rate. The baby's measurements were 2220 g of weight (5%), 45 cm of size (5%) and 33 cm of cranial perimeter 40%) Apgar score at 1 and 5 min recorded normal values (10/10).

Three weeks later the child presents hyperextension of the trunk and tremor after meal. Some days later he's hospitalized with 38.5 °C body temperature and generalized status epilepticus. A nystagmus followed by the fixity of the regard and a noisy respiration complete the clinical picture.

Physicians suspected meningitis or meningoencephalitis or an inborn metabolic disease and prescribed a broad-spectrum antibiotherapy with cefotaxime, amoxicillin, amikacin and acyclovir. A lumbar puncture and metabolic screening tests were performed. The child received Phenobarbital and Midazolam in order to stop seizures.

The initial cerebral tomography scan analysis revealed no pericerebral collection and no obvious focal lesion but a hypodense aspect of the cortical and sub-cortical layers of the parietal brain. Periventricular frontal hyperdensities and lacunar lesions in the caudate were bilaterally identified. The brain magnetic resonance imaging (MRI) detected no vascular lesion but some anomalies diffusing bilaterally in the cortical and subcortical layers of the fronto-parieto-occipital region. All these findings were consistent with a viral meningoencephalitis, but the immunological explorations of the cerebrospinal fluid have yielded rapid negative results.

2. Biochemical studies

Urinalysis with a sulfitest dipstick (Merckoquant Sulfite Test Strips, Merck KgaA, Darmstadt, Germany) at the same time with the onset of the neurological problems revealed the presence of sulfite 60 mg/l (normal < 15 mg/l). Subsequently, chromatography of urinary amino acids detected an abnormal elevated sulfocysteine 200 mmol/mol creatinine (normal < 2.7 mmol/mol creatinine) and taurine 617 mmol/mol creatinine (normal 6 to 99 mmol/mol creatinine). Conversely, plasma free cystine dropped to 1 µmol/l (normal 32–51 µmol/l) and total plasma homocysteine was undetectable (normal 32–51 µmol/l). These biochemical findings coupled with a normal level of uric acid in two blood samples 156 and 185 µmol/l (normal 120–320 µmol/l) were consistent with the diagnosis of isolated sulfite oxidase deficiency.

Indeed, sulfite oxidase activity in the cultured fibroblasts of the patient and the control was very different, 1.5 absorbance units/min/g protein and 12.5 absorbance units/min/g respectively.

3. Clinical evolution

The clinical picture deteriorated progressively. In few months, the child presented refractory epilepsy with severe encephalopathy,

Abbreviations: SUOX, sulfite oxidase

* Corresponding author at: Hôpitaux Universitaires de Strasbourg, Laboratoire de Biochimie et Biologie Moléculaire, 1 Avenue Molière, 67000 Strasbourg, France.
E-mail address: daniel.brumaru@chru-strasbourg.fr (D. Brumaru).

http://dx.doi.org/10.1016/j.ymgmr.2017.06.009
Received 11 January 2017; Received in revised form 26 June 2017; Accepted 26 June 2017
Available online 06 July 2017

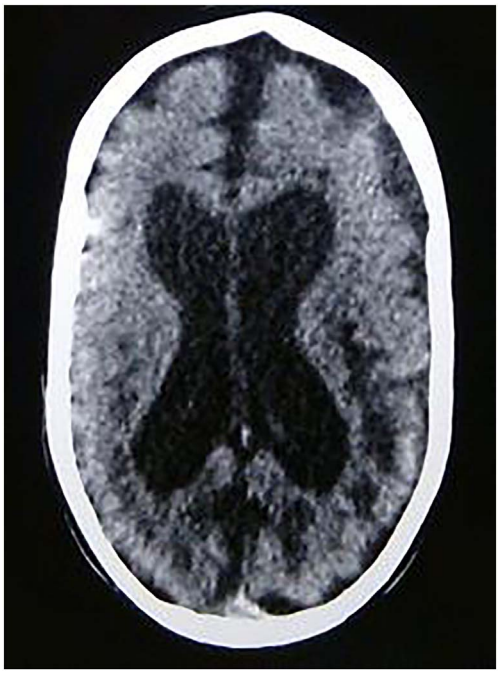

Fig. 1. Cerebral scan at the age of 20 months.

pyramidal tetraparesia, dystonia, microcephalia and failure to thrive.

At the age of 20 months, the second cerebral scan of the child revealed an important expansion of the lateral ventricles and an enlargement of the peri-cerebral spaces and of the sylvian fissure. Some hypodense lesions appeared in the periventricular white matter, surrounding the occipital horns of the lateral ventricles (Fig. 1) The child died 1 year later.

4. Molecular analysis

Genomic DNA of the affected child and of his mother was extracted from peripheral blood samples using the QIAamp Blood Kit (Qiagen) according to manufacturer's instructions. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2005. Informed consent was obtained from the mother for SUOX genetic testing for herself and her affected child. DNA was not available from the father.

The extracted genomic DNA was amplified in a hot-start-Taq polymerase chain reaction (PCR), using exon-flanking intronic primers and overlapping exonic primers for the two coding exons of SUOX gene.

PCR products were purified using Microcon-PCR filter unit (Millipore). Both DNA strands were sequenced using forward and reverse amplification primers as sequencing primers and BigDye Terminator V1.1 Cycle Sequencing Kit reagents according to manufacturer's instructions (Applied Biosystems). EDTA-ethanol purified sequencing fragments were separated by capillary electrophoresis and detected via laser-induced fluorescence on an ABI Prism 3130*xl* Genetic Analyzer (Applied Biosystems). Sequences obtained from patient samples were compared with the SUOX GenBank reference sequence (accession number AY056018) using SeqScape software V2.5 (Applied Biosystems).

5. Mutational study of SUOX gene

Sequence analysis showed that the affected child was a compound heterozygote for two novel SUOX gene mutations. A cytosine to thymine transition present in the heterozygous state was discovered at nucleotide 181, resulting in the single amino acid substitution from histidine to tyrosine at position 61 in the sulfite oxidase protein. This mutation was associated to a cytosine to guanine transversion present in the heterozygous state at nucleotide 478, resulting in the single amino acid substitution from arginine to glycine at position 160 in the protein (Fig. 2) The unaffected mother was found heterozygous for the c.181C > T;p.(H61Y) mutation and did not carry the c.478C > G;p.(R160G) mutation, indicating that both mutations identified in the affected child are located on separate alleles (Fig. 2).

Frequency of the c.181C > T;p.(H61Y) variant in the ExAC database is extremely low (0.00082%) and the c.478C > G;p.(R160G) variant is not described in the ExAC database nor in the latest versions of the NCBI dbSNP database (www.ncbi.nlm.nih.gov/snp) and the 1000 Genomes Project (www.1000genomes.org). This indicates that both

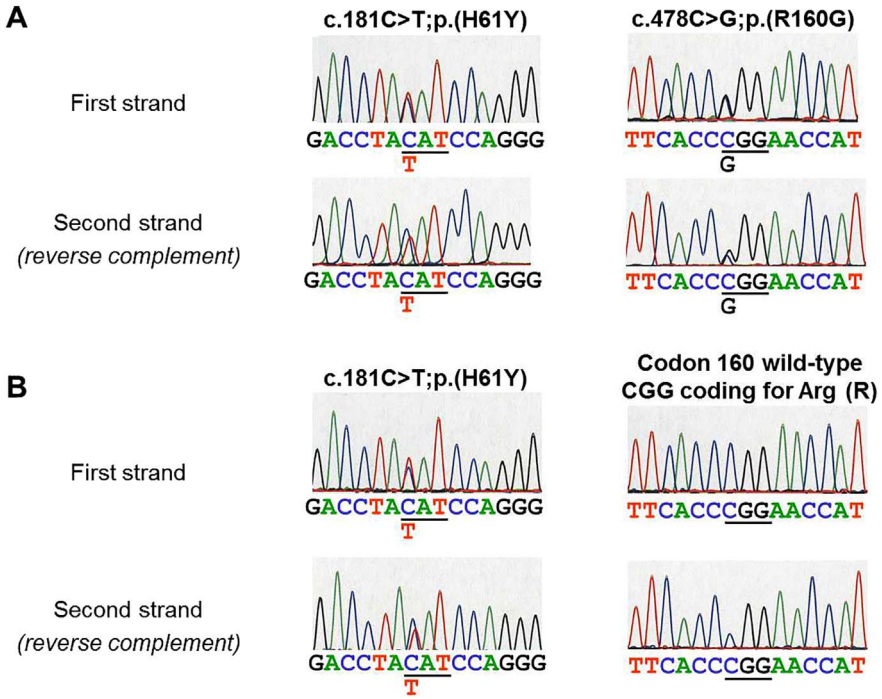

Fig. 2. SUOX gene DNA sequencing analysis. Panels A and B show sequencing results in the affected child and his mother, respectively. Sequences on both DNA strands are shown, the second strand being reversed complemented. The codon affected by the mutation is underlined. In each case, the normal sequence is listed on top and the mutated nucleotide is indicated below at the corresponding position. The resulting mutation is described at nucleotide and protein levels using HGVS (Human Genome Variation Society) standards.