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ORIGINAL ARTICLE

Isolated sulfite oxidase deficiency

Helena Claerhout[1] · Peter Witters[2,3] · Luc Régal[4] · Katrien Jansen[2] · Marie-Rose Van Hoestenberghe[5] · Jeroen Breckpot[6] · Pieter Vermeersch[1,2]

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Abstract Isolated sulfite oxidase deficiency (ISOD) is a life-threatening, autosomal recessive disease characterized by severe neurological impairment. As no long-term effective treatment is available, distinction from other treatable diseases, such as molybdenum cofactor deficiency (MoCD) type A, should be made. We reviewed 47 patients (45 previously reported in the literature). Cases were reviewed for consanguinity, sex, age at onset, death, clinical findings (including spasticity, seizures, psychomotor retardation, feeding difficulties, ectopia lentis, microcephaly), laboratory findings [urinary sulfite, S-sulfocysteine (in plasma and urine), plasma cystine, total homocysteine, uric acid, and oxypurines in urine] and radiological findings (including cerebral/cerebellar atrophy, cystic white matter changes, ventriculomegaly). We also aligned the published *SUOX* gene mutations to the reference sequence NM_000456.2. Onset occurred mostly during the first 72 h of life (57%) and within the first year of life in all but two patients (96%). All patients presented with neurological abnormalities, such as neonatal axial hypotonia and/or peripheral hypertonia (100%), (pharmacoresistant) seizures (84%), or developmental delay (97%). Feeding problems were also common. As found in our review, measurement of homocysteine in plasma, amino acids in plasma/urine, and sulfite in fresh urine supports the diagnosis of ISOD. Analysis of uric acid (plasma) and oxypurines (urine) is useful to rule out MoCD. In all patients in whom brain magnetic resonance imaging/computed tomography (MRI/CT) was performed, brain abnormalities were found. The purpose of this literature review is to provide a thorough overview of clinical, neuroimaging, biochemical, and genetic findings of patients with ISOD.

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✉ Pieter Vermeersch
pieter.vermeersch@uzleuven.be

[1] Clinical Department of Laboratory Medicine, University Hospitals Leuven, Leuven, Belgium

[2] Center for Metabolic Diseases, University Hospitals Leuven, Leuven, Belgium

[3] Clinical Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium

[4] Clinical Department of Pediatric Neurology and metabolism, UZ Brussel, Brussels, Belgium

[5] Clinical Department of Neonatal Intensive Care, Ziekenhuis Oost-Limburg, Genk, Belgium

[6] Center for Human Genetics, KU Leuven, Leuven, Belgium

Abbreviations

ISOD	Isolated sulfite oxidase deficiency
MRI	Magnetic resonance imaging
EEG	Electroencephalogram
PLEDS	Periodic lateralized epileptiform discharges
RV	Reference values
SUOX	Sulfite oxidase
MoCD	Molybdenum cofactor deficiency
XO	Xanthine oxidase
AO	Aldehyde oxidase

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Introduction

Isolated sulfite oxidase deficiency (ISOD) is a rare autosomal recessive metabolic disorder due to mutations in the sulfite oxidase (*SUOX*; OMIM 606887) gene, located on chromosome 12. Sulfite oxidase is dependent on the molybdenum cofactor. It is located in the mitochondrial intermembranous space and participates in the electron transfer from sulfites into the electron transport via cytochrome c (Tan et al. 2005). ISOD leads to a defect in the oxidation of sulfite (SO_3^{2-}), a toxic molecule produced during catabolism of sulfur-containing amino acids, such as cysteine, to sulfate (SO_4^{2-}). The disease is characterized by early onset of therapy-resistant seizures, severe psychomotor retardation, and early death. Milder and late-onset forms have also been reported (Rocha et al. 2014; Touati et al. 2000), and severity depends on the mutations and associated residual sulfite oxidase activity (Johnson et al. 2002). Neuroimaging studies typically reveal brain multicystic leukoencephalopathy and atrophy (Edwards et al. 1999; Dublin et al. 2002; Tan et al. 2005). Laboratory findings include a positive urinary sulfite test; increased urinary S-sulfocysteine, taurine, and thiosulfate; increased plasma S-sulfocysteine and taurine; normal urinary and plasma uric acid; normal plasma methionine; and lowered plasma cystine and homocysteine (Rocha et al. 2014). Heterozygous carriers of ISOD have a reduced sulfite oxidase activity of nearly 50% and are clinically asymptomatic (Johnson et al. 2002). Multiple genetic defects have been described, but the use of different reference sequences in different articles hinders interpretation of genetic findings. In this review, previously published mutations in *SUOX* were aligned to the reference sequence NM_000456.2, corresponding to a full-length sequence.

We present a thorough review of clinical, biochemical, neuroimaging (Table 1), and genetic findings (Table 2, Fig. 1) in 47 cases of ISOD. To the best of our knowledge, this is the first literature review on this subject since the publication by Tan et al. (2005). In the meantime, the number of published patients with ISOD has doubled. The purpose of this review is to guide the clinician by providing a clear overview of clinical, biochemical, neuroimaging, and genetic findings in patients with ISOD.

Patients and methods

We performed a literature search on PubMed, Human Genome Variant Society database, Limo/Libis, Science Direct, Google Scholar, and Google for previously published case reports until December 2016, including sulfite, sulfite oxidase, sulfite oxidase deficiency, isolated sulfite oxidase deficiency, case, and metabolic disorder as search terms. Twenty-two patients with ISOD were reviewed by Tan et al. (2005). We identified 23 new ISOD patients for a total of 47, including two previously unreported cases (Tan et al. 2005; Rocha et al. 2014; Lee et al. 2002; Hobson et al. 2005; Sass et al. 2010; Hoffmann et al. 2007; Seidahmed et al. 2005; Bindu et al. 2011; Balasubramaniam et al. 2012; Huang et al. 2012; Cho et al. 2013; Salih et al. 2013; Del Rizzo et al. 2013; Holder et al. 2014; Chen et al. 2014; Boyer et al. 2015; Westerlinck et al. 2014; Zaki et al. 2016; Palumbo et al. 2016) (Table 1). For all patients, sex, age at onset, death, clinical findings (spasticity, seizures, psychomotor retardation, feeding difficulties, ectopia lentis, microcephaly), radiological findings (cerebral/cerebellar atrophy, cystic white matter changes, ventriculomegaly), and laboratory findings [urinary sulfite, S-sulfocysteine (in plasma and urine), plasma cystine, total homocysteine, uric acid, and oxypurines in urine] were summarized. Previously published mutations in the *SUOX* gene leading to ISOD were aligned to the reference sequence NM_000456.2 using Mutalyzer 2.0.22 (LUMC, Leiden, The Netherlands) and Alamut® Visual 2.8–1 (Interactive Biosoftware, Rouen, France).

Results

Clinical, neuroimaging, and laboratory findings are described in Table 1 and further details in online supplementary Table 1.

Patient characteristics and age at onset

Male (23)/female (24) ratio was 0.9. Consanguinity was reported in 11 of 25 cases, which were not reported previously in the review by Tan et al. (2005). Disease onset was most often within the first 72 h of life (57%) and were within the first year of life in all but two patients (45/47; 96%): 19 cases were detected within 24 h, eight had a clinical presentation between 24 and 72 h, five showed onset between 72 h and 1 month, and there were 13 during infancy (1–12 m). Six children died within the first year of life.

Clinical presentation

No relevant clinical data could be retrieved for three patients; the remaining 44 presented with axial hypotonia and peripheral hypertonia. Thirty-seven of these patients (84%) had (pharmacoresistant) seizures. If seizures were absent, abnormal muscle tone or movements were reported. Global developmental delay was described in 32 of 33 patients (97%) undergoing psychomotor evaluation. Microcephaly was a consistent finding. Infantile or later-onset ectopia lentis occurred in 15 cases [48%; average age 17.5 (3–45) months] and spherophakia in two (6%). Sixteen patients presented with progressive feeding difficulties.

Table 1 Clinical, neuroradiological, and laboratory findings of published cases

Cases	Cases: Tan et al. 2005 (patients 1–22) (#/22 EOS)	Cases: new patient cohort (patients 23–47) (#/25 EOS)	Patients with relevant data (*n* %)
Consanguinity	Not specified	11/25 (44%)	11/25 (44%)
Gender	Male (11), female (11)	Male (12), female (13)	Male:female 23:24 (0.96)
Age of onset	≤24 h (10), >24–72 h (1), >72 h-1 month (1), infancy (9), childhood (1)	≤24 h (9), >24–72 h (7), >72 h-1 month (4), infancy (4), childhood (1)	≤24 h (19; 40%), >24–72 h (8; 17%), >72-1 month (5; 11%), infancy (13; 28%), childhood (2; 4%)
Age of death	<1 month (1), 1 month- < 1 year (2), ≥1 year (6)	<1 month (1), 1 month- < 1 year (2), ≥1 year (5)	<1 month (2; 4%), 1 month- < 1 year (4; 9%), ≥1 year (11; 24%)
Age in report	Died (9), <10 years (10), >10 years (1)	Died (8), <10 years (17)	Died (17; 37%), <10 years (27; 60%), >10 years (1; 2%)
Clinical finding			
Axial hypotonia/peripheral hypertonia	Present (21)	Present (23)	Present (44; 100%)
Abnormal movement	Present (12), absent (9)	Present (17)	Present (29; 76%), absent (9; 24%)
(Pharmacoresistant) seizures	Present (14), absent (7)	Present (23)	Present (37; 84%), absent (7; 16%)
Psychomotor retardation	Present (18), absent (1)	Present (14)	Present (32; 97%), absent (1; 3%)
Feeding difficulties	Not specified	Present (16)	Present (16; 100%)
Ectopia lentis	Present (10), absent (7), spherophakia (1)	Present (5), spherophakia (1), absent (7)	Present (15; 48%), spherophakia (2; 6%), absent (14; 45%)
Microcephaly	Not specified	Present (14)	Present (14; 100%)
Laboratory finding			
Sulfite (urine)	Positive (20), negative (1)	Positive (12), negative (1)	Positive (32; 94%), negative (2; 6%)
S-sulfocysteine (plasma)	Positive (12)	Positive (4)	Positive (16; 100%)
S-sulfocysteine (urine)	Positive (19)	Positive (14)	Positive (33; 100%)
Cystine (plasma)	Low (11)/undetectable (3)	Low (2)/undetectable (3)	Low (13; 68%)/undetectable (6; 32%)
Total homocysteine (plasma)	Not specified	Low (5)/undetectable (3)	Low (5; 63%)/undetectable (3; 37%)
Uric acid (serum/plasma)	Normal (18)	Normal (15)	Normal (33; 100%)
Oxypurines (urine)	Normal/negative (15)	Normal/negative (12)	Normal/negative (27; 100%)
Neuroimaging			
MRI/CT brain findings	Not specified	Present (24)	Present (24; 100%)
Cerebral and cerebellar atrophy	Not specified	Present (20), absent (1)	Present (20; 95%), absent (1; 5%)
Cystic white matter changes	Not specified	Present (19), absent (2)	Present (19; 90%), absent (2; 10%)
Ventriculomegaly	Not specified	Present (10), absent (1)	Present (10; 91%), absent (1; 9%)
References	1	2–17, new	

Neonatal 0–1 month, infancy >1 month to 1 year), *childhood* >1–12 years, *EOS* except otherwise specified

References: 1, Tan et al. 2005; 2, Seidahmed et al. 2005; 3, Hobson et al. 2005; 4, Hoffmann et al. 2007; 5, Sass et al. 2010; 6, Bindu et al. 2011; 7, Balasubramaniam et al. 2012; 8, Huang et al. 2012; 9, Cho et al. 2013; 10, Salih et al. 2013; 11, Del Rizzo et al. 2013; 12, Holder et al. 2014; 13, Chen et al. 2014; 14, Rocha et al. 2014; 15, Boyer et al. 2015; 16, Zaki et al. 2016; 17, Palumbo et al. 2016; new, our cases

More details about age at onset of the several findings and numerical values are available in the Supplementary table

Biochemical findings

In 32 of 34 patients (94%), sulfite was found in urine. In one patient, reported by Tan et al., urine was negative, possibly due to a false-negative result, because the urine was 2 days old (Wadman et al. 1983). The negative result in the other patient was not explained (Hoffmann et al. 2007). Both may have been false-negatives due to sulfite auto-oxidation (Wadman et al. 1983). Moreover, Wadman et al. reported false-positive results due to drugs containing a free reactive aliphatic sulfhydryl group, like N-acetyl-cysteine, mercaptamine, and dimercaprol, with the exception of penicillamine (Wadman et al. 1983). Elevated S-sulfocysteine was found in plasma (16/16) and urine (33/33). Cystine in plasma was low (under the lower limit of normal) in 13 and undetectable (below limit of detection) in six of 19 patients. If a patient has a lowered or undetectable cystine in plasma and a normal result for sulfite in urine, the detection of sulfite should be repeated on freshly catheterized urine to exclude a false-negative result. Total homocysteine levels in plasma were low in five and undetectable in three of eight patients; methionine in plasma was normal in our case and one other

Table 2 Previously published mutations in the *SUOX* gene leading to isolated sulfite oxidase deficiency (ISOD) aligned to reference sequence NM_000456.2[a]

Nucleotide	Protein	References
c.182T > C	p.Leu61Pro	(Rocha et al. 2014)
c.228 + 2 insT	splicing defect	(Bindu et al. 2011)
c.285insC	p.Glu97*	(Johnson et al. 2002)
c.287dup	p.Glu97*	(Johnson et al. 2002)
c.427C > A	p.His143Asn	(Del Rizzo et al. 2013)
c.520delG	p.Asp174Thrfs*13	(Seidahmed et al. 2005)
c.571delC	p.Gln191Serfs*13	(Rupar et al. 1996)
c.571_574delCAGC	p.Gln191Glyfs*12	(Johnson et al. 2002)
c.650G > A	p.Arg217Gln	(Lee et al. 2002; Kisker et al. 1997; Garrett et al. 1998; Lam et al. 2002)
c.734_737del	p.Leu245Profs*27	(Johnson et al. 2002)
c.772A > C	p.Ile258Leu	(Johnson et al. 2002)
c.794C > A	p.Ala265Asp	(Edwards et al. 1999; Kisker et al. 1997)
c.803G > A	p.Arg268Gln	(Johnson et al. 2002)
c.884G > A	p.Gly295Glu	(Zaki et al. 2016)
c.1084G > A	p.Gly362Ser	(Johnson et al. 2002)
c.1097G > A	p.Arg366His	(Johnson et al. 2002)
c.1098_1099delTG	p.Val367Glyfs*48	(Hoffmann et al. 2007)
c.1126C > T	p.Arg376Cys	(Johnson et al. 2002)
c.1136A > G	p.Lys379Arg	(Johnson et al. 2002; Sass et al. 2010; Holder et al. 2014)
c.1187A > G	p.Gln396Arg	(Johnson et al. 2002)
c.1200C > G	p.Tyr400*	(Johnson et al. 2002; Lee et al. 2002; Balasubramaniam et al. 2012; Chen et al. 2014; Cho et al. 2013; Huang et al. 2012)
c.1234_1235delGT	p.Val412Aspfs*5	(Salih et al. 2013)
c.1261C > T	p.Gln421*	(Johnson et al. 2002)
c.1281G > A	p.Ser427*	(Edwards et al. 1999; Kisker et al. 1997)
c.1313_1316delTAGA	p.Val438Aspfs*5	(Tan et al. 2005)
c.1348T > C	p.Trp450Arg	(Johnson et al. 2002)
c.1355G > A	p.Gly452Asp	(Chen et al. 2014)
c.1521_1524delTTGT	p.Cys508Argfs*109	(Johnson et al. 2002)
c.1523G > A	p.Cys508Tyr	(Bindu et al. 2011)
c.1585C > T	p.Arg529*	(Hoffmann et al. 2007; our cases (patient 45/46))
c.1589G > A	p.Gly530Asp	(Kisker et al. 1997)

[a] One mutation in the article by Zaki et al. 2016 [c.713G > A (p.G238Q*)] could not be aligned to this reference sequence and therefore was not included

patient (not reported in any other case). To differentiate from MoCD, uric acid in serum/plasma and oxypurines (xanthine and hypoxanthine) in plasma and/or urine should be tested (Sass et al. 2010). Uric acid levels in serum/plasma were normal in 33 of 33 patients and oxypurines in urine were normal or low in 27 of 27 patients.

Neuroimaging

In the cohort of 25 patients, not previously reviewed by Tan et al., neuroimaging by brain magnetic resonance imaging/computed tomography (MRI/CT) was performed in 24 patients. Brain abnormalities were observed in all patients either

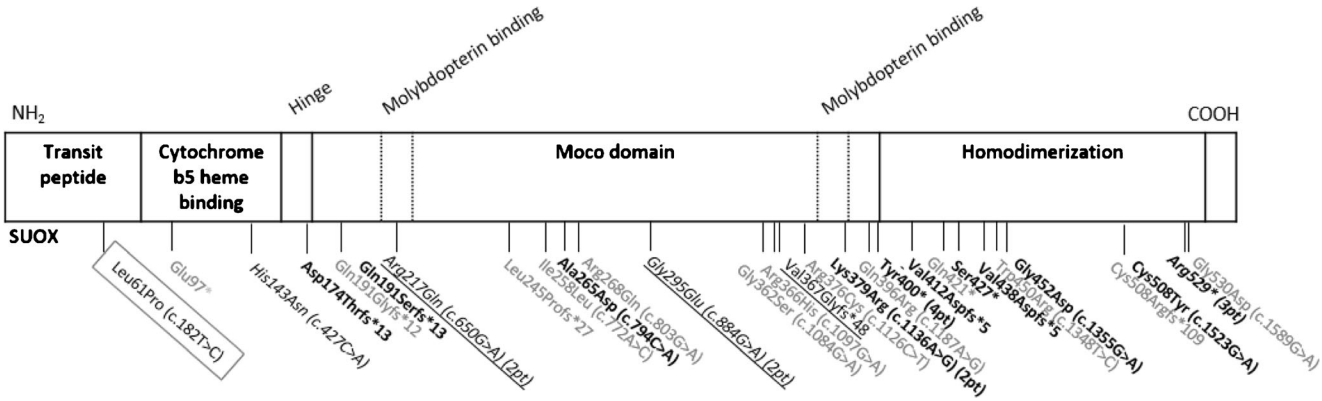

Fig. 1 Mutations in the *SUOX* gene (NM_000456.2) in isolated sulfite oxidase deficiency (ISOD) in association with symptom onset> Gray = no information about clinical presentation available; **bold** = 0–72 h, underlined = onset >72 h-1 month; italic = onset 1 month-1year; black = onset >1 year * = stop, fs = frameshift, pt. = patients

during the neonatal period (13), infancy (9), or childhood (2). Twenty patients developed cerebral and cerebellar atrophy (95%) and/or cystic white matter changes (90%) (Fig. 2). Enlarged ventricles were reported in ten patients (Fig. 2). One patient had late-onset ISOD at 4 years, showing none of the above-mentioned brain abnormalities but presenting with a thin corpus callosum and abnormal intensities of the globus pallidum (Rocha et al. 2014).

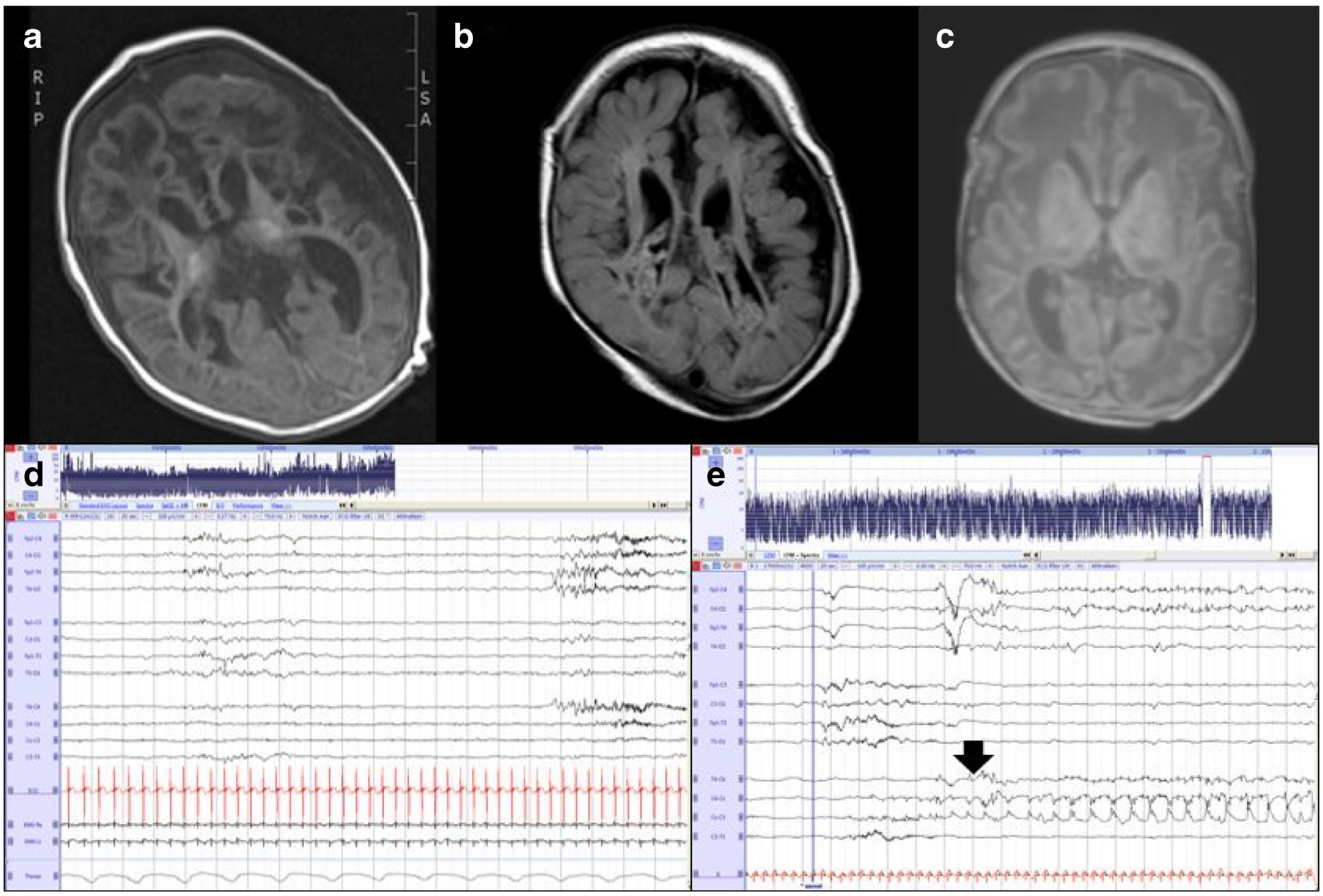

Fig. 2 Magnetic resonance imaging (MRI) and electroencephalogram (EEG). In the 23 examined patients of the 24 new-patient cohort, brain abnormalities (cerebellar and cerebral atrophy, cystic white matter changes, ventriculomegaly) were found: **a** Extended cystic degeneration of the white matter [MRI (T1) patient 45 at diagnosis]. **b** Progression of cerebral atrophy [follow-up MRI (fast low-angle inversion recovery) patient 45]. **c** Cerebral atrophy, hyperintense basal ganglia [MRI (magnetization prepared rapid acquisition gradient echo) patient 46 at diagnosis]. **d** Abnormal background pattern: burst suppression [electroencephalogram (EEG), patient 45 at diagnosis] **e** Suppressed background pattern with right central seizure activity (*arrow*) (EEG patient 46 at diagnosis)

Genetic findings

Published mutations are summarized in Table 2 and depicted in Fig. 1. One mutation was found in the transit peptide (Rocha et al. 2014), two in the N-terminal cytochrome b5 heme-binding domain (Johnson et al. 2002; Del Rizzo et al. 2013), one at the hinge (Seidahmed et al. 2005), and 15 in the Moco domain, two of which specifically target the molybdopterin-binding site (Johnson et al. 2002; Edwards et al. 1999; Lee et al. 2002; Sass et al. 2010; Hoffmann et al. 2007; Balasubramaniam et al. 2012; Holder et al. 2014; Chen et al. 2014; Kisker et al. 1997; Garrett et al. 1998; Lam et al. 2002; Cho et al. 2013; Zaki et al. 2016; Huang et al. 2012). Finally, ten mutations affect the C-terminal homodimerization domain (Johnson et al. 2002; Edwards et al. 1999; Tan et al. 2005; Hoffmann et al. 2007; Bindu et al. 2011; Salih et al. 2013; Chen et al. 2014; Kisker et al. 1997). Most patients had a homozygous mutation in the *SUOX* gene. Only in a minority of patients was compound heterozygosity found. A mutation in the *SUOX* gene, reported by Zaki et al. (2016) [c.713G > A (p.G238Q*)] could not be aligned to this reference sequence and was therefore not included in Table 2 and Fig. 1.

When we compared mutations with symptom onset (Fig. 1), we found that the only mutation reported in the transit peptide was a missense mutation in a patient with late-onset ISOD. In addition, the missense mutation causing His143Asn in the cytochrome b5 heme-binding domain was found in a patient with an onset close to 1 year, with atrophy and cystic white matter changes on MRI but no ventriculomegaly. A missense mutation in this domain might lead to milder presentations of ISOD, because a heme-deficient or heme-impaired variant might use alternative electron acceptors (such as oxygen) to complete the catalytic cycle in mitochondria. All other missense mutations, nonsense mutations, and frameshifts were found in the other domains and were associated with onset within the first year of life. Patients with missense mutations may have a later clinical presentation, while all patients with nonsense mutations or frameshifts had clinical symptoms within the first year of life.

Discussion

ISOD typically presents in the neonatal or early infantile period. Symptoms include axial hypotonia, peripheral hypertonia, abnormal movement, severe psychomotor retardation, (pharmacoresistant) seizures, feeding difficulties, microcephaly, and lens dislocation (ectopia lentis). Almost all patients presented with axial hypotonia and peripheral hypertonia. Most presented with pharmacoresistant seizures and, if absent, abnormal muscle tone and/or abnormal movements. Many patients had progressive feeding problems. Neuropathological symptoms in ISOD may mimic severe perinatal asphyxia (Hobson et al. 2005). ISOD should be included in the differential diagnosis of newborns with neonatal seizures, convulsions, abnormal movements, and abnormal EEG findings (Fig. 2). Neuroimaging by CT or MRI typically reveals several progressive neuropathological findings: white matter changes, cerebellar and cerebral atrophy, ventriculomegaly, and cystic leukomalacia (Fig. 2).

This disease is characterized by a progressive course with spasticity, intellectual deficit, microcephaly, and possible development of lens dislocation. Severity depends on mutation type and residual enzyme activity (Tan et al. 2005), but the prognosis is poor. There is no curative treatment, and although a low-methionine, low-cysteine diet has been proposed as treatment, it seems useful only in milder/late-onset forms of the disease (Rocha et al. 2014; Touati et al. 2000). Touati and colleagues reported evidence of biochemical improvement and progress in psychomotor development with no signs of neurological deterioration in two patients with a mild clinical course and late onset treated with a diet low in protein from natural foods (daily methionine intake 130–150 mg) and a synthetic amino acid mixture (50 g per day) without cystine and methionine (Touati et al. 2000). One of the two patients is still followed at Necker Hospital in Paris; her current treatment is a vegetarian, low-protein diet (30–35 g protein/day), and although she suffers from hypersomnia, she is enrolled in a vocational training program and has done several internships. The other patient was lost to follow-up at the age of six years in 2000 (personal communication Dr. Pascale de Lonlay).

In the current hypothesis, accumulation of sulfites causes mitochondrial impairment: sulfites decrease the adenosine diphosphate (ADP)-stimulated state, carbonyl cyanide m-chlorophenyl hydrazine-stimulated state, and respiratory control ratio in mitochondria respiring with glutamate and malate. In addition, sulfites inhibit glutamate and malate dehydrogenase activities in brain mitochondria, induce mitochondrial swelling, reduce mitochondrial membrane potential, Ca^{2+} retention capacity, and nicotinamide adenine dinucleotide phosphate, reduced [NAD(P)H] pool, and induce cytochrome c release in the presence of Ca^{2+} (Grings et al. 2014). Due to structural similarity to glutamate and other neuroexcitatory acidic amino acids, it was postulated that S-sulfocysteine plays a role in activation of N-methyl-D-aspartate (NMDA) receptors and contributes to the severe epilepsy in this syndrome (Tan et al. 2005). Lee et al. reported that sulfate is required in the production of sulfatides and mucopolysaccharides in neural tissue (Lee et al. 2002). However, sulfatide levels were normal in a patient with ISOD, advocating against sulfate deficiency in ISOD (Tan et al. 2005).

The mitochondrial localization is driven by an N-terminal-targeting signal and depends on the presence of molybdenum cofactor. In addition, molybdenum cofactor is required for heme cofactor integration and homodimerization of *SUOX*.

Therefore, molybdenum cofactor is considered a central component in the maturation process of the SUOX enzyme (Ono and Ito 1984; Klein and Schwarz 2012). The various RefSeq numbering in the past relates to different transcripts generated by alternative splicing. Alternative splicing of the 5' untranslated region (UTR) resulted in identical proteins. However, some alternative transcripts have different coding lengths, missing protein domains important for the maturation process, and thus of *SUOX* function (http://www.ensembl.org/Homo_sapiens/Gene/Summary?db=core;g=ENSG00000139531;r=12:55997180-56006641). To facilitate future interpretation of genetic findings, we recommend alignment of mutations in *SUOX* to the reference sequence NM_000456.2, corresponding to a full-length sequence.

No distinct segregation of groups was found when comparing the symptom onset with mutations. Most mutations were in the cytochrome b5 heme-binding, moco, and homodimerization domains. Several cases were reported with the same mutations in these domains but with a different onset. As SUOX depends on molybdenum cofactor to function, a defect in molybdenum cofactor metabolism is also associated with sulfite accumulation (and increased S-sulfocysteine levels). Therefore, MoCD causes neurotoxicity via the same mechanism, with a consequent similar clinical neurological phenotype. Two other enzymes, xanthine oxidase (XO) and aldehyde oxidase (AO), also need molybdenum cofactor for their enzymatic activity. XO catalyzes hydroxylation of hypoxanthine to xanthine and the subsequent breakdown to uric acid (Tan et al. 2005). The substrate specificity of aldehyde oxidase is much broader, and AO plays an important role in xenobiotic metabolism. A defect in XO causes xanthinuria type 1, while a combined defect in XO and AO causes xanthinuria type 2. Neither defect causes neurologic manifestations and can be asymptomatic (Terao et al. 2016). No inborn errors of metabolism due to isolated defects in AO have been reported to our knowledge.

Depending on the specific metabolic step affected in molybdenum cofactor synthesis, MoCD can be divided in three types: A, B, and C. Distinction based on clinical findings is only possible between type C, caused by mutations in gephyrin, and the other types because of the more severe neurological findings in type C. An obvious explanation can be found in the different functions of gephyrin apart from molybdenum cofactor metabolism, e.g., clustering of γ-aminobutyric acid (GABA) and glycine receptors (Tyagarajan and Fritschy 2014). It is important to distinguish ISOD from MoCD, since no specific treatment exists for ISOD whereas some patients with MoCD (type A) can be treated with cyclic pyranopterin monophosphate (cPMP) (Schwahn et al. 2015). Increased sulfite excretion in urine, elevated S-sulfocysteine in urine and plasma with low uric acid levels in plasma and urine, low total homocysteine, and increased xanthine and hypoxanthine levels in urine are suggestive for the diagnosis of MoCD (Sass et al. 2010).

In conclusion, if clinical and neuropathological findings suggest a possible SUOX deficiency, thorough laboratory diagnostics should be performed to confirm the diagnosis. As no long-term effective treatment is available for ISOD, clear distinction from treatable diseases should be made. Measurement of homocysteine in plasma, amino acids in plasma and urine (including S-sulfocysteine and cystine), and sulfite in urine are essential and quickly lead to the diagnosis. The following results are expected: low cystine and elevated S-sulfocysteine in urine and plasma, increased sulfite excretion in urine, decreased total homocysteine and normal methionine in plasma, normal uric acid levels in urine and plasma, and normal xanthine and hypoxanthine in plasma and urine (Blau et al. 2014). Sulfite must be determined on fresh urine to avoid false-negative results.

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Compliance with ethical standards

Conflict of interest H. Claerhout, P. Witters, L. Régal, K. Jansen, M.-R. Van Hoestenberghe, J. Breckpot and P. Vermeersch declare that they have no conflict of interest.

Informed consent The Ethics Committee approved this review and the inclusion of data on two new patients.

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