ORIGINAL ARTICLE

Neurologic Injury in Isolated Sulfite Oxidase Deficiency

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ABSTRACT: ***Background:*** We review clinical, neuroimaging, and genetic information on six individuals with isolated sulfite oxidase deficiency (ISOD). ***Methods:*** All patients were examined, and clinical records, biochemistry, neuroimaging, and sulfite oxidase gene (SUOX) sequencing were reviewed. ***Results:*** Data was available on six individuals from four nuclear families affected by ISOD. Each individual began to seize within the first week of life. Neurologic development was arrested at brainstem reflexes, and severe microcephaly developed rapidly. Neuroimaging within days of birth revealed hypoplasia of the cerebellum and corpus callosum and damage to the supratentorial brain looking like severe hypoxic-ischemic injury that evolved into cystic hemispheric white matter changes. Affected individuals all had elevated urinary S-sulfocysteine and normal urinary xanthine and hypoxanthine levels diagnostic of ISOD. Genetic studies confirmed SUOX mutations in four patients. ***Conclusions:*** ISOD impairs systemic sulfite metabolism, and yet this genetic disease affects only the brain with damage that is commonly confused with the clinical and radiologic features of severe hypoxic-ischemic encephalopathy.

RÉSUMÉ: Lésions neurologiques dans le déficit isolé en sulfite oxydase. ***Contexte :*** Nous avons revu l'information clinique, de neuroimagerie et génétique de 6 individus atteints d'un déficit isolé en sulfite oxydase (DISD). ***Méthode :*** Tous les patients ont été examinés et leurs dossiers ont été revus, incluant la biochimie, la neuroimagerie et le séquençage du gène de la sulfite oxydase (SUOX). ***Résultats :*** Les données de 6 individus, faisant partie de 4 familles nucléaires différentes, atteintes de SUOX, étaient disponibles. Chaque individu a commencé à présenter des crises convulsives au cours de la première semaine de vie. Le développement neurologique était limité à la présence de réflexes du tronc cérébral et une microcéphalie sévère s'installait rapidement. La neuroimagerie effectuée dans les premiers jours après la naissance a montré une hypoplasie du cervelet et du corps calleux et des dommages sus-tentoriels ressemblant à une lésion hypoxique-ischémique sévère qui évoluait vers des changements d'aspect kystique de la substance blanche hémisphérique. Les individus atteints avaient tous un taux urinaire élevé de S-sulfocystéine et un taux urinaire normal de xanthine et d'hypoxanthine, caractéristiques du DISD. Les études génétiques ont confirmé une mutation de SUOX chez 4 patients. ***Conclusions :*** Le DISD perturbe le métabolisme systémique du sulfite et pourtant cette maladie génétique n'atteint que le cerveau. Le dommage à ce niveau est souvent confondu avec les manifestations cliniques et radiologiques d'une encéphalopathie hypoxique-ischémique sévère.

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Isolated sulfite oxidase deficiency (ISOD; MIM #272300) is an autosomal recessive syndrome involving homozygous or compound heterozygous mutations in the sulfite oxidase gene (SUOX; MIM *606887) on chromosome 12q13.2-13.3. Typically, an affected infant develops seizures and feeding difficulties within the first week of life, often with axial hypotonia and limb hypertonia. Initial neuroimaging usually shows diffuse edema affecting supratentorial structures, and cystic changes later appear in the hemispheric white matter[1]. Neurologic development is generally halted at the level of brainstem reflexes, and the child remains vegetative and rapidly develops microcephaly. Death frequently occurs within the first years of life. A somewhat milder form of the disease has been reported[2,3], and some individuals survive into childhood. A related autosomal recessive disorder, molybdenum cofactor deficiency (MOCOD; MIM #252150), has similar clinical and radiologic features[4] but is due to other mutated genes affecting sulfur and uric acid metabolism[5].

The first clue to the etiology of ISOD was recognition that sulfite oxidase (SO), a soluble mitochondrial enzyme, was underactive in affected individuals[6]. Isolated sulfite oxidase deficiency patients experience an accumulation of sulfite, S-sulfocysteine, taurine, and thiosulfate and a decreased concentration of plasma cysteine[7]. They have elevated urinary

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sulfites and S-sulfocysteine, but normal urinary and plasma levels of urate, hypoxanthine, and xanthine, thus confirming the presence of ISOD and the absence of MOCOD[5,8]. Homozygous mutations were eventually documented in SUOX[7], which consists of three exons coding 466 amino acids plus a 22 residue leader that directs the protein to the mitochondrial intermembranous space.

Making a firm diagnosis of ISOD is often hampered by the early death of affected patients. Therefore, clinical reports of ISOD generally include one or two individuals with a biochemical diagnosis of the disorder[4], but the discovery that ISOD results from mutations in SUOX now permits a description of the phenotypic spectrum of an ISOD population defined both genetically and biochemically. We describe here the clinical presentations and neuroimaging of six affected individuals from four nuclear families with the biochemical signature for ISOD and/or homozygous SUOX mutations.

Materials and Methods

The medical records of six individuals with clinical, genetic, and biochemical diagnoses of ISOD from four consanguineous nuclear families (Figure 1) were reviewed. All patients were examined medically and neurologically while alive by at least one of the authors, and three patients had ophthalmologic and neuro-ophthalmologic examinations. Four patients were reported previously with less clinical and radiological detail[9,10]. Patients 1 and 2 of Family A (individuals 11 and 12 in Figure 1A) had a clinical course typical of ISOD, elevated urinary S-sulfocysteine levels (with normal xanthine and hypothanthine levels) compatible with the disease, and a novel SUOX mutation[10]. Patient 3 of Family A (individual 15 in Figure 1A) was a full sibling of Patients 1 and 2 and had the same clinical course and diagnostic biochemical testing, but he died before genetic testing was obtained. Patient 4 of Family B (individual 24 of Figure 1B) had a clinical course, biochemical testing, and SUOX mutation analysis diagnostic of ISOD[9]. Patient 5 of Family C (individual 3 in Figure 1C) also had a clinical course, biochemical testing, and SUOX mutation analysis diagnostic of ISOD. Families B and C were from the same tribe but were not closely related and were not aware of each other. Patient 6 of Family D (individual 17 in Figure 1D) had clinical, biochemical, and neuroimaging data diagnostic of ISOD, although genetic testing was not obtained.

The diagnosis of ISOD was entertained after an affected individual followed a compatible clinical course. The diagnosis was confirmed biochemically in all six patients by testing levels of urinary S-sulfocysteine, xanthine, and hypoxanthine levels by liquid chromatography-electrospray tandem mass spectroscopy[8], and genetically in four patients and their families by polymerase chain reaction amplification of three exons of the SUOX coding region and exon-intron boundaries utilizing primers described previously[9]. Five patients had brain CT and/or 1.5 Tesla MR imaging, and all available images were reviewed by a neuroradiologist (I.A.A.). All families signed informed consent approved by the appropriate Institutional Ethics Committee, and therefore these studies have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Results

Diagnostic Information

The Table details basic demographic, clinical, biochemical, and genetic information regarding all individuals. All six children had elevated urinary S-sulfocysteine levels[11]. Levels were somewhat variable in this group, but of note is the fact that only Patients 2 and 4 with levels less than 200 μm/mmol (normal ≤ 10)[8,11] survived for five or more years. All six had normal

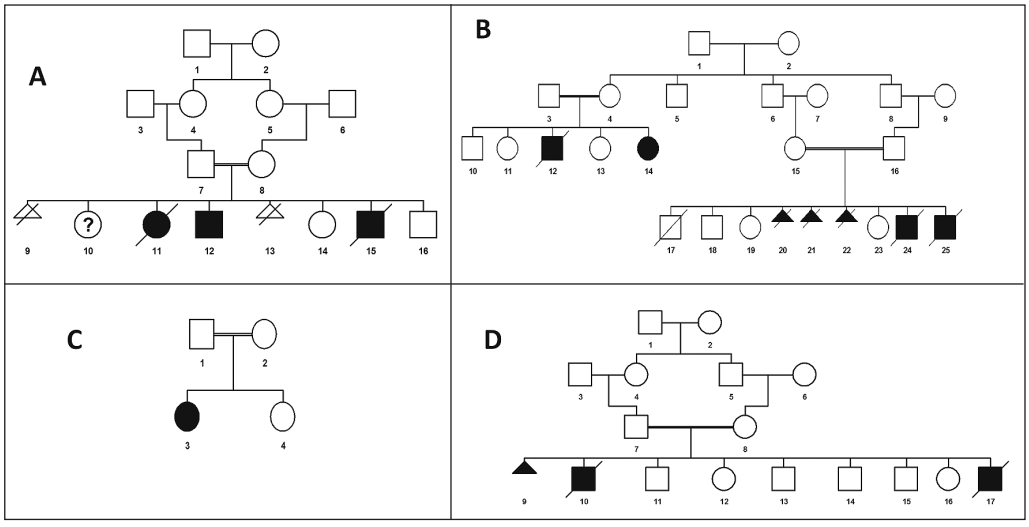

Figure 1: *Family pedigrees. In Family A, Patient 1 in this report corresponds to individual 11 on the pedigree (A). Patient 2 is individual 12, and Patient 3 is individual 15 on the pedigree. In Family B, Patient 4 is individual 24 on the pedigree (B). In Family C, Patient 5 is individual 3 on the pedigree (C). In Family D, Patient 6 is individual 17 on the pedigree (D).*

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Table: Clinical, biochemical and genetic data

Patient	1	2	3	4	5	6
Family	A	A	A	B	C	D
Sex	Female	Male	Male	Male	Female	Male
Onset seizures (days of life)	1	3	2	2	2	1
Seizure type	Tonic/clonic	Tonic/clonic	Tonic/clonic	Tonic/clonic	Partial and migrating	Partial and tonic/clonic
Urinary S-sulfocysteine (µm/mmol)	326	144	Elevated	305	222	356
Urinary Xanthine (µm/mmol)	34.9	23	Normal	21	12.9	17
Urinary Hypoxanthine (µm/mmol)	53	21	Normal	8	5.8	4
***SUOX* mutation**	c.1232-1233delT	c.1232-1233delT		c.520delG	c.520delG	
Head circumference later (age; SD)	39 cm (10mo; 2SD)	44 cm (6y; 5SD)		39 cm (30 mo 3SD)	38 cm (45 days)	
Dislocated lens (age)	Yes	Yes	NA	No at 7 mo	NA	NA
Time of Neuroimaging	CT at 11 months	CT at 4 days; MRI at 13 days; CT & MRI at 10 months	No imaging	CT at 4 & 14 days; MRI at 7 months	CT at 45 days	MRI at 7 months; CT at 10 months
Current status	Died at 14 mo	Alive at 9 years	Died on day 15	Died at 5 years	Lost to follow-up	Died at 2 years

NA=not ascertained; mo=months; y-years; SD=standard deviation; CT=computed tomogram; MRI=magnetic resonance imaging

urinary xanthine and hypoxanthine levels typical of ISOD but not MOCOD[8,12].

SUOX sequencing was performed on two individuals from Family A (Patients 1 and 2 in the Table) together with their parents and fifty normal controls of the same ethnicity [Salih, 2013 #10]. The SUOX gene had a homozygous two base successive deletion c.1232-1233delTG in the two affected children that was heterozygous in both parents and was not detected in 100 chromosomes from individuals of matching ethnicity. This deletion will lead to a frame shift and to truncation of the molybdopterin binding domain of the sulfite oxidase protein. SUOX sequencing was also performed in Patients 4[9] and 5 together with their parents and control individuals. These patients both had a single nucleotide deletion c.520delG that is predicted to cause a frame shift at amino acid 117 of the hinge region between the heme-binding domain and the molybdo-pterin- and dimerizing-binding domains[9]. This generates 12 new codons followed by a stop codon, causing a mutant, catalytically inactive SO protein that is composed of 128 amino acids and contains an intact leader sequence and heme-binding domain with total truncation of the molybdo-pterin- and dimerizing-binding domains.

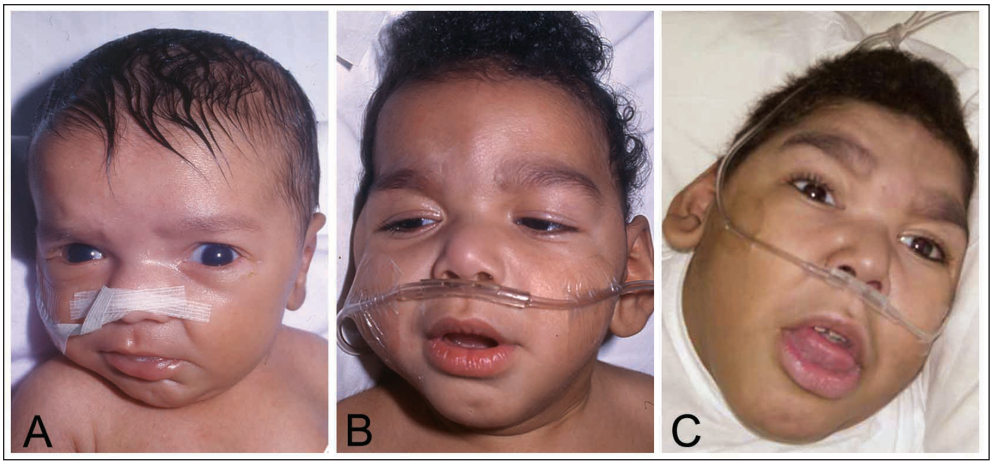

Figure 2: *Progression of microcephaly. Patient 2 at age 7 days, 10 months, and 7 years documenting progression of microcephaly and facial dysmorphism associated with severe damage to supratentorial brain.*

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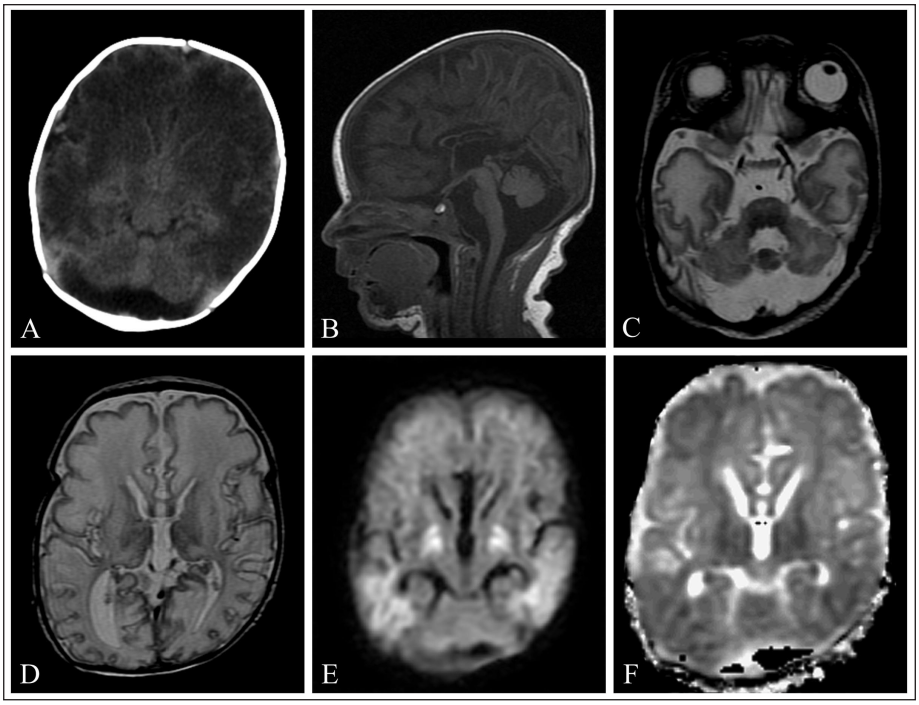

Figure 3: *Acute neuroimaging changes. Patient 2 (A) CT of the brain at the age 4 days showing diffuse brain swelling causing effacement of cerebral sulci and compression of the lateral ventricles. Hemispheric white matter and basal ganglia have remarkably low attenuation. Less remarkable low attenuation is evident in the thalami and cerebellum. (B-F) MR images of the brain at age 13 days. (B) Sagittal T1-weighted MR image showing low signal in the hemispheric white matter with relatively bright, thin cortex, extremely thin corpus callosum, and large cisternal magna. (C and D) Axial T2-weighted MR images showing bilateral and symmetrically abnormally high signal in the hemispheric white matter, basal ganglia, and posterolateral thalami. The cerebellar hemispheres are equally hypoplastic, and less striking high signal changes are seen in the cerebellar white matter. (E) Diffusion-weighted MR image and (F) apparent diffusion coefficient (ADC) map demonstrating symmetric diffusion restriction in basal ganglia, thalami, and occipito-temporal area.*

Clinical Data

Patient 1 (Family A-11) was born at term but began to have multifocal seizures on the third day of life and was subsequently diagnosed biochemically as having ISOD. She died at age 14 months of a respiratory infection. Patient 2 (Family A-12), a boy, was born at term by cesarean section to avoid any possibility of perinatal hypoxia but nevertheless began to have multifocal seizures on the second day of life and subsequently developed the neuroimaging appearance of diffuse hypoxia-ischemia followed by microcephaly and facial dysmorphism (Figure 2). He is currently vegetative at age nine years. Patient 3 (Family A-15) was a boy with biochemically proven ISOD who began to seize on the second day of life and died on day 15. The family also had two abortions.

Patient 4 (Family B-24) was born to a consanguineous couple[9] and had maternal cousins with ISOD[11]. He began to seize at age two days and by age eight months was microcephalic and diffusely spastic with only brainstem reflexes. This couple also had three spontaneous abortions and one son (Family B-17) who died at age one month of unknown cause. Patient 5 (Family C-3) was born normally to a consanguineous couple after an uncomplicated pregnancy and developed multifocal partial seizures on the second day of life. She was first admitted at age 45 days and was discharged after three weeks with seizures under good control but was lost to follow-up. Patient 6 (Family D-17) was also the product of a normal pregnancy and delivery but was brought back to hospital after one day because of abnormal movements. He had multiple admissions for seizure control and respiratory distress, and by age four months he had not achieved any developmental milestones and was diffusely spastic. His family had one spontaneous abortion.

Pregnancies and deliveries of ISOD children were normal except for one patient delivered by caesarian section in order to avoid any possibility of perinatal hypoxia. Affected children were born with normal APGAR scores, without dysmorphism, and with height, weight, and cranial circumference within the normal range. They seemed clinically normal for the first hours of life until poor feeding became apparent and multifocal partial seizures appeared. When done in the perinatal period, electrolytes, liver function tests, urine evaluation for reducing substances, phenylketonuria, mucopolysaccharidoses, and very long chain fatty acids, and other standard newborn testing were normal.

All affected children failed to develop normal motor milestones, being almost immobile and unable to turn over or sit throughout life. Patients gained height and weight normally but became severely microcephalic over the first six months of life and developed a typical progressive facial dysmorphism (Figure 2). All failed to interact with the environment or make spontaneous movements other than an exaggerated startle reaction and abnormal limb and eye movements compatible with episodic focal seizures. All patients appropriately evaluated were behaviorally blind with moderate optic atrophy and no retinal or optic disk edema. Two eventually developed ectopia lentis[13]. Ocular motility was grossly normal, but all had central hypotonia with hypertonic limbs and diffuse hyperreflexia.

Perinatal CT and MRI scans shortly after onset of seizures were available in three patients. Initial scans always showed profound, diffuse cerebral hemispheric white matter edema with loss of grey-white differentiation and sparing of the cerebral cortex (Figure 3). Basal ganglia, thalami, and deep cerebral nuclei were edematous shortly after birth in a distinctive pattern that would be atypical for even severe perinatal hypoxia-

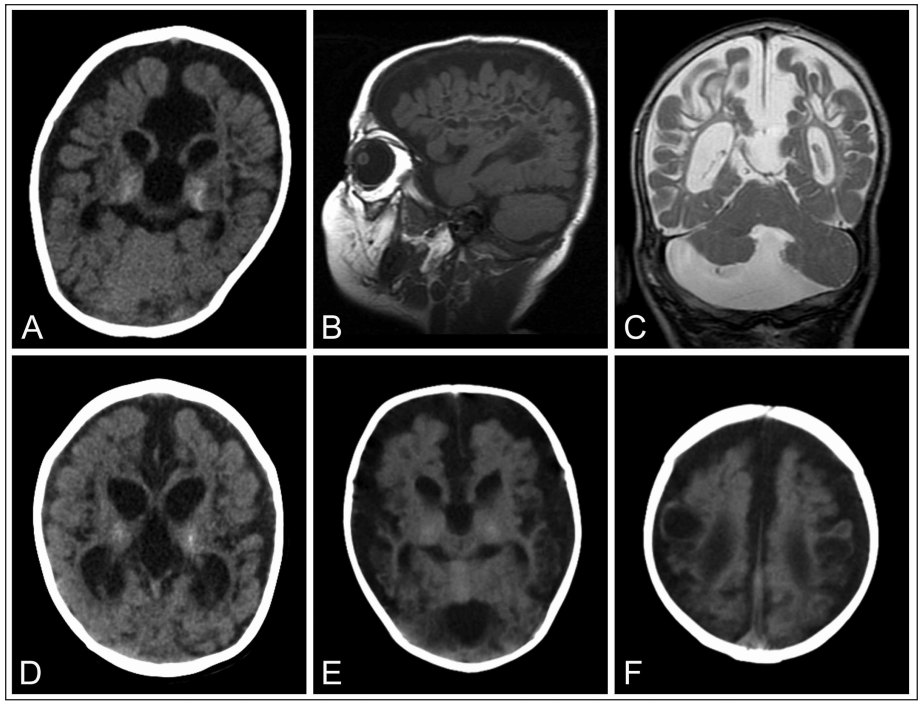

Figure 4: *Chronic neuroimaging changes. Patient 2 (A-C) follow-up neuroimaging at the age of 10 months. (A) Axial CT image of the brain demonstrating progressive hemispheric white matter loss with subsequent enlargement of the lateral ventricles, cisterns, sulci, and fissures. Cysts are seen in the hemispheric white matter and basal ganglia. Faint calcification is evident in both thalami. (B) Sagittal T1-weighted and (C) coronal T2-weighted MR images showing loss and cystic replacement of the white matter of the frontal and parietal lobes with less remarkable changes in the temporal and occipital lobes. Large cisterna magna and right cerebellar hypoplasia are seen on (C). Patient 1 (D) follow-up axial CT image of the brain at the age of 11 months showing similar changes seen in patient 1 (A). Patient 5 (E & F) follow-up axial CT image of the brain at the age of 45 days showing a slightly different pattern of brain damage. The cerebral cortex is more involved than the white matter (E) with large ventricles, subarachnoid spaces, and cisterna magna. Large subcortical cysts are seen at the brain convexity (F).*

ischemia. Diffusion-weighted images in Patient 2 at the age of 14 days revealed diffusion restriction in basal ganglia, thalami, and temporal and occipital lobes implying ongoing injury rather than just a perinatal insult. Patients were born with a hypoplastic cerebellum (vermis and/or hemisphere), and the corpus callosum was thin from genu to splenium, implying a primary developmental abnormality of these structures. Cerebral cortex appeared immature in one term baby with a simplified gyral pattern and sulci that were unusually shallow anteriorly and of relatively normal depth posteriorly. The combination of neonatal seizures and neuroimaging with characteristics thought compatible with a severe hypoxic-ischemic encephalopathy (HIE) made severe perinatal ischemia the initial diagnosis in the first affected child of each consanguineous couple reported here. Post-perinatal imaging was available in five patients. Over a period of months, the hemispheric white matter injury became cystic with abnormal white matter signal on brain MRI implying white matter loss and gliosis (Figure 4). Thalami and basal ganglia eventually developed volume loss and tiny calcifications in some patients, but there were no major progressive changes in the appearance of posterior fossa structures. Observations on neuroimaging performed after age one to two months were not distinguishable from cystic leukomalacia; therefore, a high index of neuroradiologic suspicion was important early on in the course of ISOD.

Discussion

We describe six individuals with ISOD from four consanguineous families who had neonatal onset of intractable seizures, failed to develop any motor milestones, and rapidly became microcephalic. In general, they were felt to have a clinical presentation compatible with severe HIE, although birth trauma and low Apgar scores were not documented. Possible diagnoses that could be confused with ISOD or HIE include other metabolic disorders[14] such as glycine encephalopathy (nonketotic hyperglycinemia)[15], pyridoxine-responsive seizures[16], and mitochondrial disorders[17]. These diagnoses can be differentiated by their characteristic biochemical, EEG, and/or imaging features[15-18]. All of these ISOD patients had diffuse brain edema in the neonatal period leading to cystic changes in cerebral white matter within months. All had increased urinary S-sulfocysteine levels and normal urinary xanthine and hypoxanthine levels diagnostic of ISOD[8] and not typical of MOCOD, a related genetic disorder of sulfate and uric acid metabolism[5]. Where tested, the SUOX gene had homozygous mutations, while parents were heterozygous for the same mutations. Therefore, this group of individuals met clinical, biochemical, and genetic criteria for ISOD.

The nervous system experienced the brunt of the syndrome in these patients, implying a special developmental and metabolic vulnerability of the human brain to this abnormality of sulfite metabolism. Neuroimaging revealed fulminant damage occurring to cerebral hemispheric white matter in the days and weeks after birth and speaks to the presence of an acute process following delivery[19,20]. The reported neuropathology of ISOD is consistent with these observations and with the clinical observations of seizures and extremely stunted neurologic development. In autopsies of affected children from infancy[21] or early childhood[1,7], deep cerebral white matter was markedly damaged with diffuse loss of myelin and axons and pronounced glial proliferation resulting in a striking cystic appearance of the hemispheres. The cerebral cortex, thalami, and basal ganglia had scattered areas of necrosis of varying ages with cysts and

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gliosis[22]. Retinal ganglion cells and nerve fiber layer were badly damaged, and the optic nerves had severe loss of myelin and axons. These neuropathologic observations generally apply to MOCOD[23] as well as ISOD, firmly linking elevated systemic sulfite levels to this clinical picture and to neuroimaging and neuropathology with an appearance compatible with brain ischemia.

Sulfites are generally not thought to be toxic and, in fact, are used as preservatives and antioxidants in a number of pharmaceuticals[24]; however, certain sulfur-containing compounds are known to associated with ischemic brain damage. Sulfites in a dexamethasone preparation were reported to increase neuronal loss and neurotoxicity of excitotoxic agents in premature infants[25]. Sulfur dioxide is an air pollutant that has been linked to increasing stroke mortality[26], possibly via mechanisms including excessive glutamate-mediated excitotoxicity[27]. The chemical warfare agent sulfur mustard[28] and the odorless industrial byproduct carbonyl sulfide[29] are both known to cause brain damage. Finally, stem cell therapy often involves delivery of stem cells in a 10% solution of the cryopreservative dimethyl sulfoxide, which may in part be responsible for strokes that can occur in this setting[30].

In addition, both *in vitro* and *in vivo* experiments have also linked sulfites to neuronal damage. Increasing sulfite concentrations in rat neuronal tissue culture strongly decrease biosynthesis of adenosine-triphosphate (ATP) from oxidation of glutamate in a dose dependent fashion because of glutamate dehydrogenase (GDH) inhibition, resulting in decreased intracellular ATP, increased reactive oxygen species, and cell death[31]. Glutamate dehydrogenase is widely distributed in the human brain[32] in a fashion that may imply that brain ATP production after birth is considerably dependent on glutamate oxidation[31]. A neonate with ISOD may be particularly vulnerable to elevated sulfite concentrations because sulfite oxidase activity in human brain is an order of magnitude lower than in rat brain[33].

The fulminant injury to both grey and white matter structures of the cerebral hemispheres occurs in the days after birth in severe ISOD. One possible interpretation of this time course is that the maternal circulation may partially regulate sulfite levels *in utero* until birth isolates the neonatal circulation and permits a rise in systemic sulfite levels in ISOD. Abruptly increased sulfite levels after birth may cause inhibition of GDH, decreased brain ATP concentrations, elevated extracellular glutamate levels, and increased excitotoxity during the perinatal period when periventricular white matter is particularly vulnerable both anatomically and metabolically[34]. In addition, S-sulfocysteine, an abnormal sulfur metabolite present in ISOD, has a molecular structure similar to glutamate and causes brain damage similar to other excitotoxic compounds when administered to newborn and adult rats[35]. These biochemical changes may precipitate a cycle of decreased energy supply leading to white matter damage[36] through a pathophysiologic mechanism comparable to that of an hypoxic-ischemic insult and eventually to a neonatal brain injury that appears similar to severe birth asphyxia.

Although the neuroimaging characteristics of the neuropathologic process causing cortical white matter edema and destruction in ISOD were very similar to those of HIE[19-20,22], there are certain important neuroimaging differences. The extensive white matter edema noted in these patients was grossly consistent with severe birth trauma, especially that occurring in a premature baby[37]. However, thalamic involvement in HIE tends to be ventral and lateral, while it was posterior and lateral when present in these ISOD patients. Diffusion abnormalities in ischemia are expected to normalize after one week, while these changes remained longer in Patient 2, implying ongoing brain damage after birth. In addition, ISOD patients were born with hypoplasia of the cerebellum, the corpus callosum, and the anterior cerebral cortex[9,11] that implies an effect of SUOX mutations on the proliferation and/or migration of certain neuronal groups during *in utero* development.

ISOD patients had some non-neurologic clinical problems as well, including severe asthma (four patients)[22], abdominal distress (three patients), and ocular lens dislocation (two patients)[22,38], while three of these four families had spontaneous abortions and premature deliveries leading to death. Increased sulfite levels may be responsible for asthma in a fashion analogous to asthmatic patients who react adversely to increased dietary sulfites[39]. Dietary sulfites also increase activity in the parasympathetic nervous system and stimulate the release of histamine and other mediators as a consequence of mast cell degranulation[40], providing a potential partial explanation for muscle spasm and tissue edema that might lead to pyloric stenosis. The sulfite radical is capable of damaging DNA, lipids, and proteins[41] and may cause ectopia lentis by a direct effect on zonules. Therefore, asthma, abdominal distress, and lens dislocation in ISOD may be related in part to a direct effect of elevated sulfite concentration in blood and interstitial tissues. Spontaneous abortions suggest fetal maldevelopment or injury relatively early in gestation that are not compatible with life.

Sulfite levels can likely be altered by diet[3], pharmacologic manipulation[42], or dialysis. Unfortunately, these treatments might have little long-term effect on an infant with ISOD given pre-natal brain development abnormalities and the severity of this lifelong condition. Finally, the clinical course of ISOD patients may be complicated to some extent by a direct effect of SUOX mutations on metabolism of other sulfur-containing endogenous compounds. These include glutathione, which is critical in anti-oxidant defense[43]; L-cysteine, which potentiates glutamate toxicity *in vivo*[44]; and taurine, which modulates neurotransmitter release, calcium homeostasis, and osmoregulation[45]. Some component of the clinical course and neuropathology of ISOD might relate to these other biochemical changes that are specific to ISOD rather than to brain energy metabolism.

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