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Delineating the phenotypic spectrum of sulfite oxidase and molybdenum cofactor deficiency

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Abstract

Objective

To define the phenotypic spectrum of isolated sulfite oxidase (ISOD) and molybdenum cofactor deficiency (MoCD), aiming to promote timely diagnosis and assist in future clinical trial design.

Methods

We analyzed clinical, radiographic, biochemical, and genetic data from 146 patients reported in the literature.

Results

We stratified patients into 2 phenotypic subgroups based on clinical and radiographic characteristics. In the first (Class I), patients presented early in life (age 1–50 days) with acute onset of neurologic symptoms and development of diffuse brain injury with cystic leukomalacia. Patients in the second subgroup (Class II) presented later in life (age 30 days–23 years) with prominent movement abnormalities and selective injury of the basal ganglia and cerebellum. A significant difference in survival estimates correlated with milder disease severity among Class II patients. Substantial overlap in sulfur-containing metabolite levels prevented discrimination of subgroups based on diagnostic biomarkers, but genotype-phenotype correlations suggested that residual SUOX activity may contribute to milder phenotypes.

Conclusions

Patients with SUOX and MoCD gravitate toward 1 of 2 distinct clinicoradiographic profiles. Patient stratification may help promote accurate diagnosis, prognostication, and aid in the design of future clinical trials.

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Glossary

CI = confidence interval; **cPMP** = cyclic pyranopterin monophosphate; **GPHN** = gephyrin; **ISOD** = isolated sulfite oxidase deficiency; **MoCD** = molybdenum cofactor deficiency; **NS** = not specified; **SSC** = S-sulfocysteine; **SUOX** = sulfite oxidase.

Isolated sulfite oxidase deficiency (ISOD) and molybdenum cofactor deficiency (MoCD) are inherited neurodegenerative conditions that comprise the known disorders of sulfite metabolism.[1] Sulfite oxidase (SUOX) is a molybdenum cofactor–dependent enzyme, and loss of its activity is necessary and sufficient to cause the neurodegenerative phenotype of ISOD or MoCD. Although patients with ISOD carry biallelic pathogenic variants in *SUOX*, patients with MoCD harbor pathogenic variants in one of the molybdenum cofactor synthetic enzymes, MOCS1, MOCS2, gephyrin (GPHN), or MOCS3.

Classically, patients with ISOD and MoCD present in the first days of life with clinicoradiographic features that mimic neonatal hypoxic-ischemic encephalopathy.[2–4] Milder phenotypic variants have also emerged in scattered case reports; however, a comprehensive analysis of phenotypic variants has not been performed, and the phenotypic spectrum of disease remains poorly defined.

Advances in therapeutic options for ISOD and MoCD have produced an urgent need to delineate the phenotypic spectrum of patients, which will be essential in guiding clinical trial design.[5–7] Low patient numbers have been a major hurdle to studying these ultra-rare disorders. To overcome this limitation, we leveraged the clinicoradiographic congruency of ISOD and MoCD and systematically evaluated a cohort of 146 published patients from both disorders. We directed our efforts at defining the clinicoradiographic features that distinguish phenotypic subgroups and investigated subgroup associated differences in survival, age at neurologic symptom onset, diagnostic biomarker levels, and genotype-phenotype correlations.

Methods

Literature review and definition of variables

We performed literature searches on PubMed using the terms "sulfite oxidase deficiency" and "molybdenum cofactor deficiency," encompassing the time frame up to July 2017. Searches were conducted in August of 2017. We excluded articles with insufficient data. We also excluded articles that only described MoCD type A patients treated with cyclic pyranopterin monophosphate (cPMP), as this treatment could alter the natural history of disease. In total, we identified 93 articles (published 1967–2017) for review (figure e-1, links.lww.com/NXG/A284, and table e-1, links.lww.com/NXG/A286). From those reports, we identified 146 patients for analysis after excluding duplicate reports of the same patient and additional MoCD type A patients treated with cPMP (table e-1). Patients with MoCD type B who received cPMP therapy were included as the treatment should not affect the underlying metabolic defect.

We extracted the following variables: age at onset of neurologic symptoms, age at the time of report, age at death, mode of diagnosis, ethnicity of the patient (only if explicitly stated), examination findings, brain MRI results, urine and plasma levels of sulfite, S-sulfocysteine (SSC), thiosulfate, taurine, L-cysteine/L-cystine, xanthine, and uric acid, and genetic diagnoses. We defined the age at onset of neurologic symptoms as the age at which seizures, infantile spasms, hyperekplexia, appendicular hypertonia, dystonia, opisthotonos, extrapyramidal signs not otherwise specified, ataxia, or acute hemiparesis were first observed or diagnosed or when the patient first presented with concerns for developmental delay. Plasma metabolite levels were all converted to μmol/L, and urine metabolite levels converted to mmol/molCr (urine). Quantitative measurements reported below the threshold of detection were recorded as a value of zero. Plasma metabolite levels normalized to creatinine or urine metabolite values not normalized to creatinine were excluded.

To minimize bias, brain MRI findings were only recorded as "present" if explicitly described or identifiable in published radiographic images. If information regarding time was semiquantitative, we took a conservative approach and used the following definitions: "at birth" = day 1, "first week" = day 7, and "first year" = 1 year.

Statistical analysis

Patient demographics, clinical characteristics, and radiographic findings were summarized descriptively. Survival was defined as the time elapsed between birth and time of death. Patients were censored at the age at the time of report if they were still alive. We used the Kaplan-Meier method to describe survival, and the log-rank test was used to assess differences in survival between patient subgroups. To compare metabolite levels between subgroups, we used single values from each patient. If multiple values were reported, we used the average. Measurements made during or after dietary restriction of cysteine and/or methionine or chelation therapy were excluded. Because of the low number of data points for each metabolite, normality of the sample populations could not be assessed. Median values for each metabolite were calculated for Class I and Class II subgroups. We calculated the power of a nonparametric Mann-Whitney test to detect the difference in median values and only considered the test acceptable if the power was ≥0.8. To calculate Spearman correlation coefficients between metabolite levels, we pooled concomitant measurements of multiple metabolites made in individual patients across the entire cohort. Multiple measurements from the same patient made during or after dietary restriction of methionine and/or cysteine were included to capture dynamic, synchronous changes between different metabolites. We performed all statistical analysis with Prism 8, GraphPad software.

Data availability

All data extracted from the literature that was used for the analyses reported in this article will be made freely available on request from the corresponding author. The data will be available for 5 years from the time of publication and may be requested by any clinician or researcher.

Results

Demographic information and diagnoses for the patient cohort are listed in table 1. The prevalence of disease was roughly equal between sexes, and patients originated from a pan-ethnic distribution. Because available data varied between reports, patients had to be excluded from specific analyses. The corresponding sample size (N) is indicated with each analysis.

Confirmation of diagnosis

A diagnosis of ISOD or MoCD was confirmed by genetic sequencing of *SUOX* (ISOD; OMIM:606887), *MOCS1* (MoCD type A; OMIM:603707), *MOCS2* (MoCD type B; OMIM:603708), *MOCS3*, or *GPHN* (MoCD type C; OMIM: 603930) in 62 (42%) patients, whereas diagnosis based on biochemical abnormalities was made in 84 (58%) patients. Additional biochemical characterization to determine MoCD subtype was not performed in 43 (29%) patients who were labeled MoCD not specified (NS). All MoCD NS patients had elevated levels of xanthine and hypoxanthine and/or low levels of uric acid to rule out ISOD. SUOX activity was assayed in fibroblasts from 49 patients and reported as undetectable in 47 samples. Fibroblasts from an additional 2 patients had measurable SUOX activity.[8,9] Diagnosis in these patients was made by sequencing of the *GPHN* and *MOCS3* genes and identifying a pattern of biochemical abnormalities consistent with MoCD.

Stratification of patients by clinicoradiographic presentation

We evaluated our entire cohort and observed that patients strongly gravitated toward 2 unique clinicoradiographic profiles. The first (Class I) embodied patients who presented acutely with abrupt onset of neurologic symptoms and evidence of diffuse brain injury on brain MRI or CT. The second class (Class II) embodied patients who presented with neurologic symptoms that emerged gradually or episodically against a background of normal or mildly delayed development and evidence of region-restricted brain injury on imaging.

Based on the authors' consensus opinion, we stratified patients into the class that was most consistent with their available data (table e-1, links.lww.com/NXG/A286). A larger portion of patients with ISOD (25%) than patients with MoCD (13%) were stratified into Class II (table e-2, links.lww.com/NXG/A287). The most commonly reported clinical features in Class I and Class II patients are compared in table 2. Brain MRI abnormalities are compared in table 3; these only included MRI abnormalities in Class I patients reported >20 days after their initial neurologic symptom onset, as data from an equivalent acute or subacute phase of disease in Class II patients were lacking. Within each class, the frequency of clinical features and brain MRI abnormalities were similar between patients with ISOD and MoCD, except for atrophy/hypoplasia of the corpus callosum and cerebellum, which were more frequently reported in patients with ISOD (table e-3, links.lww.com/NXG/A288, and table e-4, links.lww.com/NXG/A289).

Table 1 Characteristics of the ISOD and MoCD patient cohort (146 patients)

Population characteristics	N	%
Sex		
Male	66	45
Female	60	41
Not reported	20	14
Ethnicity		
Middle Eastern	34	23
European[a]	12	8
Asian	9	6
Indian	6	4
North African	6	4
British Isles	4	3
Central/South American	3	2
Eastern European	1	1
Ashkenazi Jewish	1	1
West African	1	1
Not reported	69	47
Diagnosis		
ISOD	52	36
MoCD type A	25	17
MoCD type B	23	16
MoCD type C	2	1
MOCS 3	1	1
MoCD NS	43	29

Abbreviations: ISOD = isolated sulfite oxidase deficiency; MoCD = molybdenum cofactor deficiency; NS = not specified.
[a] Central or Western European; NS = genotype not reported; diagnosis based on biochemical abnormalities.

Age at neurologic symptom onset

The median age at first symptom onset was 1 day (interquartile range: 1–2.5 days) for Class I (N = 113) and 11.5 months (interquartile range: 6 months to 1.5 years) for Class II (N = 25) subgroups. Because age at symptom onset did not affect patient stratification, we found a slight overlap between Class I and Class II patients (figure 1A).

Table 2 Clinical features in Class I and Class II patient subgroups

	Class I (N = 121)		Class II (N = 25)	
Disease feature	**N**	**%**	**N**	**%**
Motor/tone				
Axial hypotonia	55	45	13	52
Appendicular hypertonia	76	63	14	54
Quadriparesis	15	12	3	12
Acute hemiparesis	0	0	4	16
Extrapyramidal				
Opisthotonos	18	15	2	8
Choreoathetosis	0	0	10	40
Dystonia	1	1	8	32
Extrapyramidal NOS	8	7	2	8
Cerebellar				
Ataxia	0	0	7	28
Nystagmus	4	3	1	4
Paroxysmal events				
Seizures	109	90	10	40
Infantile spasms	3	2	0	0
Hyperekplexia	10	8	0	0
Ocular				
Ectopic lentis	24	20	11	44
Enophthalmos	11	9	0	0

Abbreviation: NOS = not otherwise specified.

Survival estimations

In the Class I subgroup, 68 patients (58%) were alive, and 50 patients (42%) were deceased at the time of publication. In the Class II subgroup, 21 patients (84%) were alive, and 4 (16%) were deceased. The median age of survival for Class I was 2.5 years (N = 118), but it could not be calculated for Class II (N = 25) as survival exceeded 50% at the longest time point (figure 2, A and B). Survival was statistically shorter in the Class I subgroup ($p < 0.0001$, log-rank test).

Table 3 Brain MRI abnormalities in Class I and Class II patients

	Class I (N = 39)		Class II (N = 13)	
Abnormality	**N**	**%**	**N**	**%**
Diffuse cerebral atrophy	39	100	3	21
Cavitary subcortical leukomalacia	24	62	0	0
Corpus callosum atrophy/hypoplasia	10	26	4	29
Isolated cystic or T2 hyperintense lesions in the globus pallidus	0	0	9	69
Cerebellar T2 hyperintense lesions	0	0	2	14
Cerebellar or vermal atrophy/hypoplasia	9	23	5	38

Biochemical abnormalities

SUOX is a molybdenum cofactor–dependent enzyme that oxidizes sulfite to sulfate in the terminal step of sulfur-containing amino acid and hydrogen sulfide metabolism (figure e-2, links.lww.com/NXG/A285). For a review on these pathways, please see Kohl et al.[10] Commonly reported biochemical abnormalities in patients with ISOD and MoCD include elevated levels of urine and plasma sulfite, SSC, thiosulfate, and taurine, whereas L-cystine is diminished. Abnormalities unique to MoCD included elevated xanthine and decreased uric acid levels due to the inactivation of xanthine oxidase (a molybdenum cofactor–dependent enzyme). Across the entire cohort, all extracted laboratory values were consistent with the expected pattern of abnormalities.

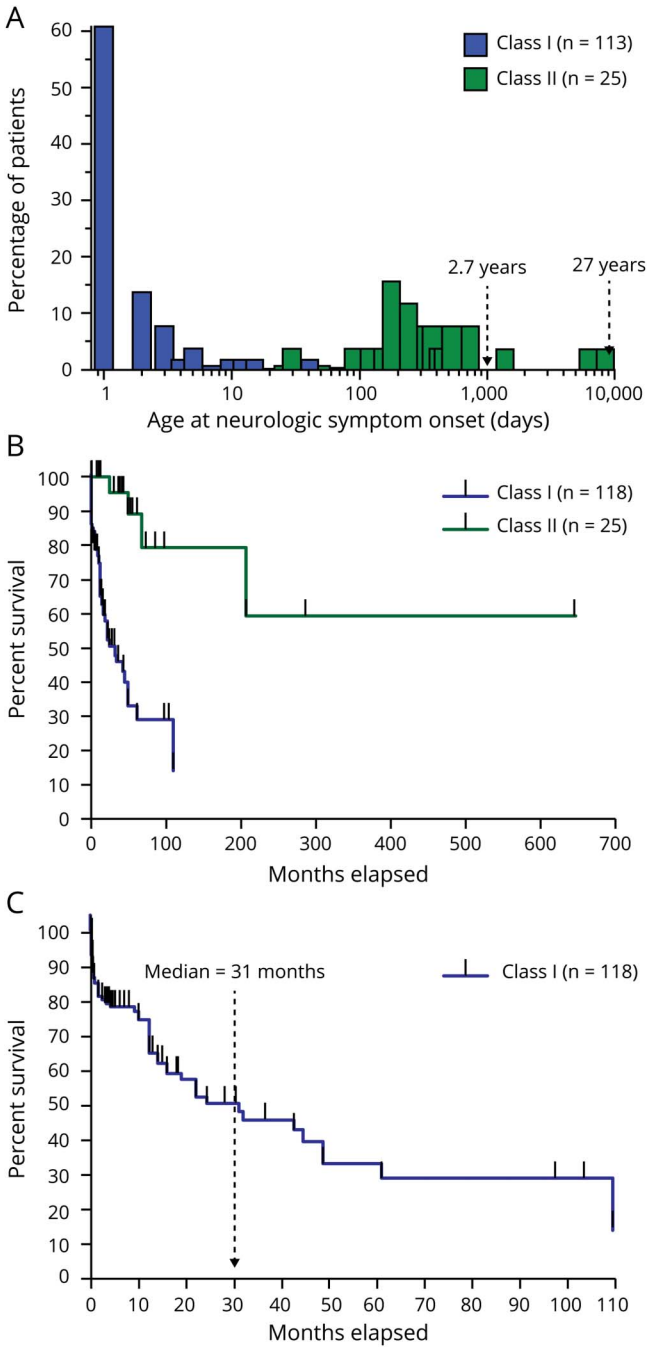
Metabolite levels were compared between Class I and Class II subgroups to assess for an indirect correlation with the contrasting survival time. Urine and plasma metabolite levels from Class I and Class II subgroups demonstrated an appreciable overlap (figure 2, A–H). Because of the low number of reported values for Class II patients, we could not test for a significant difference between subgroup medians (for all metabolites, a nonparametric Mann-Whitney test with alpha = 0.05 would have a power <0.5).

Because sulfite and SSC exert direct neurotoxic effects on the CNS, these metabolites are potential biomarkers for assessing treatment efficacy in ISOD and MoCD. Unfortunately, aqueous sulfite is unstable, limiting its utility; however, if sulfite or SSC levels correlate with other sulfur-containing metabolites, additional biomarkers for monitoring treatment efficacy could be developed. To this end, we calculated Spearman correlation coefficients between metabolite levels concomitantly measured in individual patients across our entire cohort. SSC levels in urine and plasma correlated (r = 0.7, 95% confidence interval [CI] = 0.332–0.890, N = 17) as expected. Correlations were also identified between plasma cystine and SSC (urine SSC: r = −0.6, 95% CI = −0.851 to −0.178, N = 17; plasma SSC: r = −0.58, 95% CI = −0.840 to −0.102, N = 16), urine taurine and SSC (urine SSC: r = 0.54, 95% CI = 0.164–0.772, N = 25; plasma SSC: r = 0.88, 95% CI = 0.613–0.968, N = 12), and urine sulfite and urine thiosulfate (r = 0.5, 95% CI = 0.005–0.809, N = 16).

Genotype-phenotype correlations

Genotypes were reported for 52 Class I patients (43%) and 10 Class II patients (40%). Allelic variants uniquely segregated between patient subgroups with 1 exception (table e-5, links.lww.com/NXG/A290). The 38 allelic variants unique to Class I patients included 14 missense (37%), 10 frameshift (26%), 8 nonsense (21%), and 6 splice site (16%) mutations that were

Figure 1 Age at neurologic symptom onset and estimated survival distributions for Class I and Class II patients with isolated sulfite oxidase deficiency and molybdenum cofactor deficiency



(A) Age at onset of neurologic symptoms for each patient subgroup. The percentage of patients was calculated separately for Class I and Class II. (B) Survival estimates for Class I and Class II subgroups. A tick mark represents censored patients. The median age of survival for Class I patients was 31 months (C). The median age of survival for Class II was not calculated as survival remained above 50%.

predicted to disrupt function of the associated gene product. The 10 allelic variants unique to Class II patients included 7 missense (70%), 1 frameshift (10%), 1 nonsense (10%), and 1 splice site (10%) mutation. The frameshift and nonsense mutations were both identified in patients compound heterozygous for a point mutation in the same gene.[11,12] One allelic variant in *MOCS1* (R222_G223insR) was found both in a Class I and a Class II patient who were homozygous for the mutation.

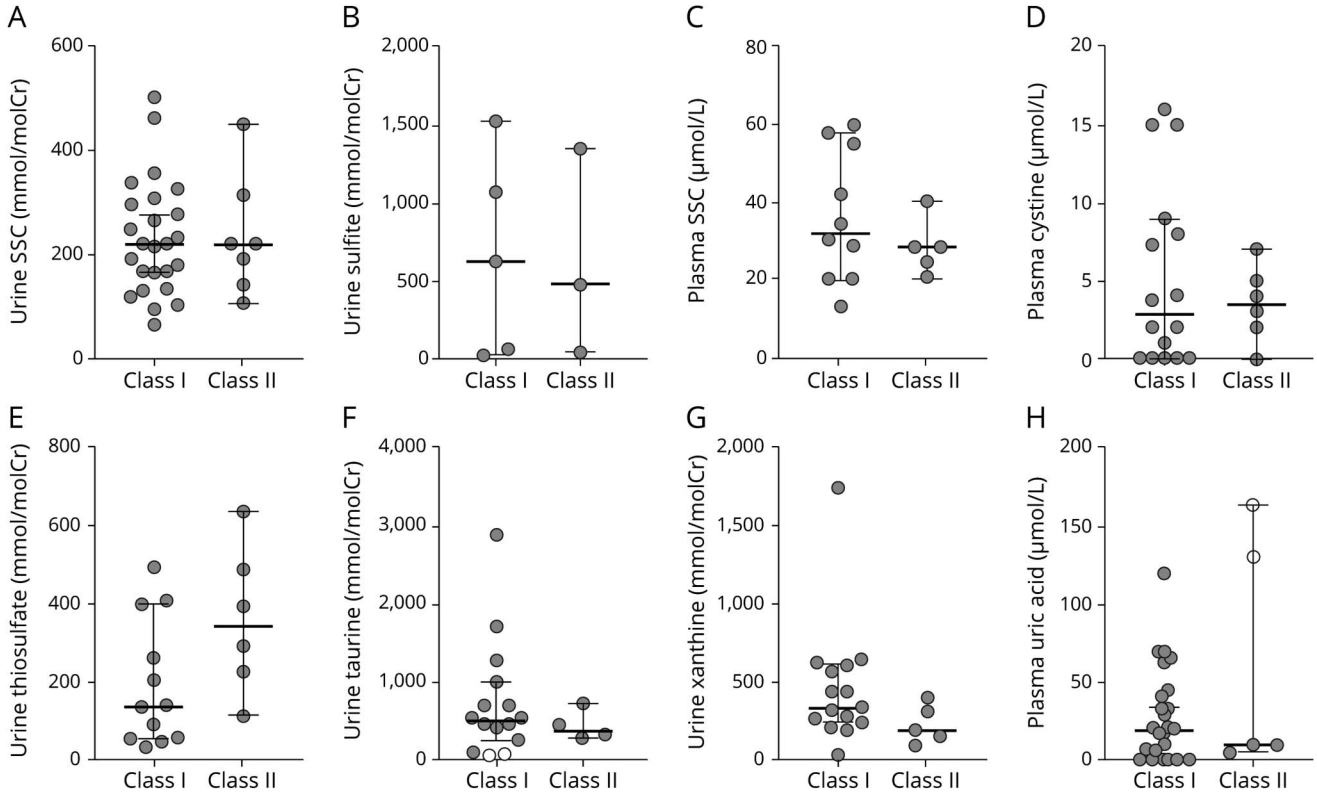
Discussion

We discerned 2 subgroups of patients with ISOD and MoCD based on their clinicoradiographic features. These subgroups roughly correspond to the "early-onset" or "severe" (Class I) and "late-onset" or "mild" (Class II) terms that have been variably used in the literature.[1,13,14] The validity of our approach is supported by the contrasting survival estimates and genotype-phenotype associations that emerged. Dividing patients with ISOD and MoCD into 2 classes has clinical utility for several reasons. First, emphasizing the unique features of Class II patients will help raise awareness among clinicians and promote diagnosis. Because limited data suggest that dietary restriction of sulfur-containing amino acids may have an impact on neurologic symptoms severity or disease progression in mildly affected patients, an accurate diagnosis would make a potentially beneficial intervention available to patients.[8,15–17] Second, clinicoradiographic features may predict neurologic outcomes better than the age at neurologic symptom onset. We identified Class I patients who first presented as late as 40–50 days of life.[18,19] These patients exhibited an acute onset of neurologic symptoms and signs of severe forebrain injury that may not have been expected from their later onset. Finally, formal recognition of mild phenotypic variants will assist with patient stratification and identification of appropriate endpoints in future clinical trials.

We observed little phenotypic variation across patients in Class I, and severe neurologic impairment was reported in all patients with available follow-up. The narrow phenotypic spectrum and pattern of injury suggest a global susceptibility of the forebrain and cerebellum driven mainly by genotype. In contrast, we observed a higher degree of phenotypic variability across Class II patients. Reported outcomes ranged from static neurologic symptoms to progressive neurologic impairment with periodic decompensations in function. The wider phenotypic spectrum and pattern of neurologic injury in these patients suggest a selective susceptibility of the basal ganglia and cerebellum driven by a complex interaction of genotype, environment, and developmental context.

Despite a limited sample size, we were able to appreciate an association between genotypes and patient subgroups. Extensive analyses of disease-associated missense mutations in SUOX have been performed.[20–24] Karakas and Kisker place these variants into 3 categories: (1) mutations affecting the active site, (2) mutations destabilizing coordination of the molybdenum cofactor, and (3) mutations disrupting dimerization. The mutations associated with Class I patients with ISOD fit into these categories and are predicted to abolish SUOX activity. In contrast, the L61P[25] and H143N[15]

Figure 2 Sulfur-containing metabolite levels reported in Class I and Class II patients with isolated sulfite oxidase deficiency and MoCD



All sulfur metabolite levels measured in urine (A, B, E, and F) and plasma (C and D) showed substantial overlap between Class I and Class II subgroups. Urine xanthine and plasma uric acid levels in patients with MoCD also showed substantial overlap between Class I and Class II patients (G and H). Horizontal bars represent the median value, and brackets encompass the 25th and 75th quartiles. Solid circles indicate a metabolite value outside of the reported reference range, whereas an open circle indicates a value within the reported reference range. Low sample numbers precluded assessment for a statistically significant difference in median values between subgroups. MoCD = molybdenum cofactor deficiency; SSC = S-sulfocysteine.

mutations found in 2 Class II patients with ISOD lie in the hydrophobic region of the mitochondrial targeting domain and cytochrome-b5 heme-binding domain, respectively. These variants may retain some enzymatic activity explaining the milder associated phenotypes. This notion is supported by the identification of the R217Q (previously R160Q) mutation in 2 Class II patients with ISOD. The R217Q mutation in SUOX modifies the binding site for sulfite,[26] but retains residual activity.[27]

Similar structural analyses have been performed for the molybdenum cofactor synthetic enzymes, and data suggest that variants associated with Class I patients with MoCD abolish enzymatic activity.[28–34] While this article was in preparation, an atypical a case of MoCD type A was reported in which a novel MOCS1 mutation (S442 fs) resulted in the translation of a truncated peptide that was expressed at low levels but retained catalytic activity.[35] This patient had a mild clinical course that could have resulted from SUOX activity supported by residual molybdenum cofactor production.

Despite the observed associations between genotype and patient subgroups, it is important to note that genotype does not fully explain reported phenotypes. Disease severity can significantly vary between affected siblings, highlighting the contribution of the environment or unappreciated differences in genetic background.[11,14,36]

We found a large degree of overlap in metabolite levels between subgroups. Low sample numbers precluded our ability to test for significant differences between median metabolite values; however, the overlap observed is sufficient to suggest that metabolite levels alone may not directly correlate with disease severity. Data currently support a disease model in which sulfite and SSC are mainly produced in peripheral tissues and then accumulate in the CNS, where they directly injury neural tissue.[6,7] To interpret the prognostic significance of circulating metabolite levels, a better understanding of their origin(s), distribution kinetics, and quantitative relationship to CNS damage are still needed.

Despite a limited understanding of how plasma and urine levels of sulfite and SSC relate to the degree of CNS injury, their utility as biomarkers to assess treatment efficacy is strongly implied by their direct role in disease pathogenesis. SSC is a stable in solution, while aqueous sulfite rapidly oxidizes to sulfate,

limiting its utility as a clinical biomarker. Our analysis showed that urine sulfite correlated with plasma cystine and urine thiosulfate levels. As these molecules are stable in solution, they may act as proxy measures of sulfite. Moreover, analyzing combinations of metabolites in relation to disease severity may prove more efficacious in predicting treatment efficacy than single metabolites alone. Clinical trials with cPMP substitution therapy should generate large data sets of sulfur metabolite levels necessary for deeper analysis in the future.

Several important limitations are inherent in the design of our study. First, it was not possible to measure the true frequency of a clinical or radiographic finding based on a collection of reports originating from different institutions. Variations in clinical examinations or the specific focus of a case report could influence which disease features were reported, thereby introducing an ascertainment bias. Different imaging protocols and MRI machines between institutions and the lack of blinded interpretation also obscure the true frequency of radiographic abnormalities. Furthermore, the quality and completeness of clinical data varied between case reports, and it was often not possible to conclude whether a clinical or radiographic feature was absent vs not reported in the article. As such, we analyzed the frequency with which a symptom or radiographic finding was reported, although we believe that this still holds value as a proxy measure of true frequency.

Several factors could have influenced the accuracy of survival estimates. First, the publications included in our cohort ranged from 1967 to 2017, a period over which technology and the quality of medical substantially evolved, potentially improving outcomes in more recently reported patients. Second, our cohort consisted of patients around the world. Although this enriched our data pool, regional differences in standard of care may have influenced outcomes. Finally, patient deaths were not frequently reported. This particularly affected analysis of the Class II subgroup where patient survival remained above 50%, precluding estimation of median survival time.

Because we pooled sulfur metabolite values that were measured in different laboratories, there is an element of interlaboratory variability in our analysis that we are unable to quantify. Future prospective studies centered on assessing the efficacy of experimental treatments will be well poised to centralize the measurement of metabolite levels and provide a more accurate comparison of levels between patient subgroups.

In this report, we provide a quantitative analysis of phenotypic subgroups in ISOD and MoCD. These results have diagnostic and prognostic implications that may help guide clinical care and inform the design of future clinical trials.

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Disclosure

A.L. Misko consults for Origin Biosciences, a pharmaceutical company developing cPMP substitution therapy for patients with molybdenum cofactor deficiency type A. This study does not address the effects or efficacy of cPMP therapy and was not supported by commercial funding. Y. Liang and J.B. Kohl do not have any conflicts to disclose. F. Eichler has participated in an advisory board for Origin Biosciences. Go to Neurology.org/NG for full disclosure.

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Ye Lian, MS	Massachusetts General Hospital and Harvard Medical School, Boston	Interpreted data and revised the manuscript for intellectual content
Joshua B. Kohl, PhD	University of Cologne, Germany	Interpreted data and revised the manuscript for intellectual content
Florian Eichler, MD	Massachusetts General Hospital and Harvard Medical School, Boston	Interpreted data and revised the manuscript for intellectual content

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