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Not your typical newborn screen for X-ALD: Outcomes from Washington State

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Background: X-linked adrenoleukodystrophy (X-ALD) is an X-linked genetic condition caused by pathogenic variants in the *ABCD1* gene that primarily affects the adrenal glands and nervous system. The known clinical manifestations include isolated adrenal insufficiency, childhood cerebral disease, adult-onset adrenomyeloneuropathy with or without cerebral involvement in hemizygotes, and myelopathy in heterozygotes. X-ALD was added to the recommended uniform screening panel in February of 2016, and Washington State began screening for X-ALD in March of 2018. Washington State's newborn screening program typically measures metabolites on at least two dried blood spot specimens, collected at approximately 24 hours of life and at 1-2 weeks of life.
Case presentation: Here we present unusual cases that screened positive for X-ALD on Washington State newborn screening and discuss possible implications including potential causes for false positive screens, unexpected clinical progression, challenges with further workup of ambiguous biochemical and molecular results, and unexpected results from family cascade testing.
Conclusion: We have encountered multiple unexpected clinical scenarios in individuals who screened positive for X-ALD, as expected when introducing a new condition to newborn screening. These cases outline important implications to consider in the newborn screening follow-up and clinical care for these individuals.

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Biochem for the Win! The added value of biochemical genetic testing for diagnosis and variant interpretation in the genomic era

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Background: Diseases of intracellular accumulation of carbohydrate-containing compounds, including the broad categories of oligosaccharidoses, mucopolysaccharidoses, and congenital disorders of (de)glycosylation, have a wide range of intra- and inter-disease phenotypic variability and severity, as well as considerable overlap with other genetic conditions (eg, developmental delay, abnormal tone, short stature, cardiac disease, etc.). As accessibility and evidence-based support for broad molecular genetic screening/testing continues to increase, a molecular-first testing approach is often used in the evaluation of patients with multiple nonspecific clinical features. While revolutionary and diagnostic in many cases, this testing strategy often supersedes biochemical evaluation with the incorrect assumption that broad molecular testing will identify inherited metabolic disorders (IMDs) if present. Here we present three cases illustrating limitations of broad molecular testing in evaluating patients for IMDs, while also showcasing the diagnostic utility of biochemical testing in disorders of macromolecule accumulation using traditional and advanced mass spectrometry methods.
Case presentation: Case 1: Trio exome sequencing was ordered on a toddler-aged girl with global developmental delay, hypotonia, leukodystrophy identified by brain MRI, and bilateral cataracts. Exome sequencing revealed multiple monoallelic likely-pathogenic variants, including a single paternally inherited variant in *NGLY1* (NM_018297.4:c.1764_1785del), associated with autosomal recessive congenital disorder of deglycosylation. Urine glycomic profiling by LC-MS/MS was ordered by a separate provider and revealed abnormal excretion of GlcNAc-N-Asn and NeuAc-Gal-GlcNAc-Asn, consistent with a diagnosis of NGLY1 deficiency. These results were communicated to both providers and altered the clinical interpretation and subsequent genetic counseling for the patient and family. A pathogenic variant in *NGLY1* on the maternal allele has yet to be identified.
Case 2: A healthy adult man with tall stature was found to have a hemizygous likely-pathogenic missense variant in *IDS* (NM_000202.6:c.1439C>T) by expanded preconception carrier screening, reported as consistent with the diagnosis of X-linked mucopolysaccharidosis, type 2 (MPS II). Clinical evaluation revealed a lack of features suggestive of MPS II and biochemical laboratory studies were ordered for further clarification. Quantitative urine glycosaminoglycans (GAGs) were within normal limits (1.0 mg/mmol Cr, reference <13) and no abnormal bands were detected by thin layer chromatography; iduronate-2-sulfatase enzyme activity was also normal (390 nmol/4hr/mL, reference 155-1082). Given these biochemical results, this individual is not considered to have MPS II but will continue to follow with a prenatal genetic counselor due the possibility of mosaicism and/or variant reclassification in the future.
Case 3: The results of trio exome sequencing performed in another country were provided to the on-call physicians of a toddler-aged boy upon admission for hypoxemia in the setting of global developmental delay, microcephaly with normal brain MRI, hypotonia, mild transaminitis, and dysmorphic features. Translation of the report revealed several monoallelic variants of uncertain significance (VUSs) in addition to biallelic heterozygous missense VUSs in *MOGS* (NM_006302.3:c.[1619G>A];[2126T>C]), associated with autosomal recessive congenital disorder of glycosylation, type 2b (MOGS-CDG). Both variants were absent in the literature and the Genome Aggregation Database (gnomAD), and prediction tool outputs ranged from possibly damaging to disease causing. Urine glycomic profiling by LC-MS/MS revealed marked elevation of a compound annotated as Glc_3-Man, consistent with a diagnosis of MOGS-CDG.
Conclusion: Biochemical genetic assays are valuable in evaluating individuals for IMDs, alone or in concert with molecular genetic testing. While currently in the genomic era, advances in mass spectrometry have led to improved detection of clinically-relevant compounds, further aiding in the identification of individuals with IMDs, including genetic disorders of macromolecule accumulation. When coupled with molecular testing, biochemical evaluation can be a complementary and relatively-inexpensive asset in providing a more comprehensive genetic evaluation, as well as *in vivo* functional data for variant interpretation.

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