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Case Report

Biochemically Confirmed Metachromatic Leukodystrophy in a Child Initially Diagnosed as Cerebral Palsy: A Radiological Case Report

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Abstract

Metachromatic leukodystrophy (MLD) is a progressive lysosomal storage disorder in which brain magnetic resonance imaging (MRI) may provide the first clue to an inherited white matter disease. We report a 6-year-old girl with developmental delay from early life, a history of minor perinatal distress with an otherwise reassuring neonatal course, longstanding spasticity, inability to walk independently, and caregiver-reported developmental regression beginning at approximately 18 months of age. She had previously been labeled as having cerebral palsy and was referred for brain MRI after epileptic seizures. MRI demonstrated bilateral, symmetric, confluent T2- and fluid-attenuated inversion recovery hyperintensity of the periventricular and deep cerebral white matter, most pronounced in the parieto-occipital regions with frontal involvement and relative sparing of the subcortical U-fibers, without corresponding diffusion restriction. This distribution suggested an inherited leukodystrophy, particularly MLD. The diagnosis was subsequently confirmed biochemically by reduced leukocyte arylsulfatase A activity together with increased urinary sulfatide excretion, the latter distinguishing true enzyme deficiency from arylsulfatase A pseudodeficiency. Molecular testing was not performed but is recommended for family genetic counseling. This case illustrates that true developmental regression is not a feature of the static encephalopathy underlying cerebral palsy and should prompt renewed investigation, and that a characteristic MRI pattern can direct the biochemical testing required to confirm MLD.

Keywords: *Metachromatic Leukodystrophy; Developmental Regression; Epilepsy; Magnetic Resonance Imaging; Cerebral Palsy*

Abbreviations

ARSA: Arylsulfatase A; FLAIR: Fluid-Attenuated Inversion Recovery; MLD: Metachromatic Leukodystrophy; MRI: Magnetic Resonance Imaging

Introduction

Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal sphingolipid storage disorder caused most commonly by deficient arylsulfatase A activity, leading to sulfatide accumulation and progressive demyelination in the central and peripheral nervous systems [1]. Clinical subtypes are classified according to age at symptom onset. The late-infantile form generally begins before 3 years of

age and is characterized by rapid motor regression, whereas juvenile and adult forms may initially present with cognitive, behavioral, or motor abnormalities [1,2].

Brain MRI is central to the evaluation of suspected leukodystrophy because lesion distribution can narrow the differential diagnosis and direct laboratory testing. Nevertheless, MRI is not sufficient to establish MLD. Current recommendations emphasize biochemical confirmation through arylsulfatase A activity and urinary sulfatide analysis, with molecular testing used to identify pathogenic ARSA variants and support genetic counseling [3].

The distinction from cerebral palsy can be particularly challenging in children with early motor impairment and a history of perinatal events. Cerebral palsy describes permanent motor and postural disorders attributable to a non-progressive disturbance of the developing fetal or infant brain [4]. A genuine loss of previously acquired abilities therefore represents a diagnostic warning sign and should prompt reconsideration of a purely static encephalopathy. We describe a child previously labeled as having cerebral palsy in whom developmental regression, epilepsy, and a symmetric white matter MRI pattern led to biochemical testing that confirmed MLD, illustrating how imaging can orient the diagnostic pathway.

Case Presentation

A 6-year-old girl was referred for brain MRI following epileptic seizures. She was born at term after a pregnancy complicated by premature rupture of membranes. Delivery was vaginal, in the setting of fetal distress with an abnormal fetal heart rate and a nuchal cord. Apgar scores were 5, 7, and 10 at 1, 5, and 10 minutes, respectively, and birth anthropometric measurements were within normal limits. She was admitted to the neonatal unit for four days; no neonatal seizures, hypoxic-ischemic encephalopathy, hypoglycemia, severe infection, or significant jaundice were documented, and neonatal cranial ultrasonography was normal. Despite this largely reassuring neonatal course, she showed delayed neurodevelopment from early life, with an initial motor phenotype dominated by stiffness and progressive spasticity, and she never achieved independent walking. On this basis, she had previously been considered to have cerebral palsy.

According to the caregivers, her course was not entirely static. At approximately 18 months of age, they observed a definite decline with loss of previously acquired developmental abilities rather than simple developmental stagnation. This progressive component, together with the later occurrence of seizures, raised concern for an underlying disorder beyond a fixed perinatal motor injury.

MRI findings

Axial fluid-attenuated inversion recovery and axial and coronal T2-weighted images demonstrated bilateral, symmetric, confluent hyperintensity involving the periventricular and deep cerebral white matter. The abnormalities were most conspicuous in the parieto-occipital regions, with additional frontal involvement. The subcortical U-fibers were relatively spared (Figure 1). No corresponding restriction was identified on diffusion-weighted imaging.

No definite signal abnormality of the deep gray nuclei or corpus callosum was seen on the available examination. No definite tigroid pattern, focal mass effect, or overt cerebral atrophy was identified. The symmetrical confluent distribution and relative sparing of the subcortical white matter suggested an inherited leukodystrophy, with MLD as the leading radiological possibility. Given the perinatal history, chronic hypoxic-ischemic white matter injury was initially considered, although the benign neonatal course and normal cranial ultrasonography made a significant destructive perinatal injury unlikely.

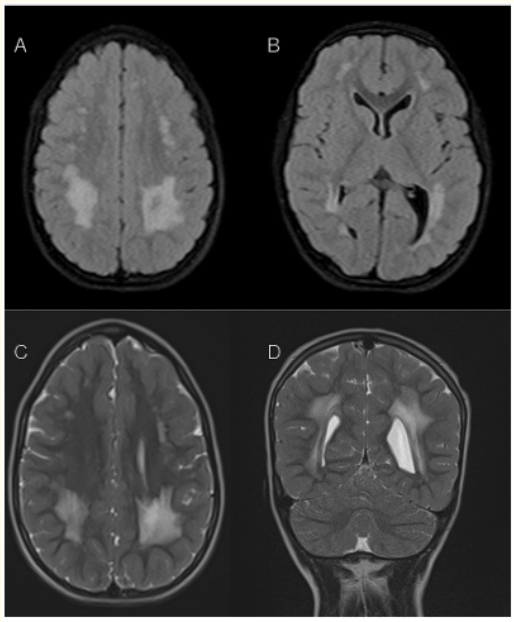

Figure 1: *Brain MRI in a 6-year-old girl with developmental regression and seizures. Axial FLAIR images (A, B) and axial (C) and coronal (D) T2-weighted images demonstrate bilateral, symmetric, confluent hyperintensity of the periventricular and deep white matter, with parieto-occipital predominance and frontal extension. The subcortical U-fibers are relatively spared. No definite signal abnormality of the deep gray nuclei or corpus callosum is seen on the displayed images.*

Subsequent biochemical testing demonstrated reduced leukocyte arylsulfatase A activity together with increased urinary sulfatide excretion, confirming metachromatic leukodystrophy. The combination of low enzyme activity and elevated urinary sulfatides is important because it distinguishes true arylsulfatase A deficiency from pseudodeficiency, in which enzyme activity is low but sulfatide excretion remains normal. Molecular analysis of ARSA and nerve conduction studies were not performed, and no serial MRI was available; molecular testing is nonetheless recommended to support genetic counseling and carrier detection within the family.

Discussion

The interpretation of pediatric white matter abnormalities requires a pattern-based approach incorporating lesion symmetry, confluence, predominant location, involvement of specific tracts, and the presence of enhancement, rarefaction, or atrophy [5]. MLD typically produces bilateral, symmetric, confluent T2 hyperintensity in the periventricular and deep white matter, often with posterior predominance and relative sparing of the subcortical U-fibers during earlier stages [5,6]. Radially oriented bands or dots of relatively preserved tissue can create the characteristic tigroid or leopard-skin appearance. With progression, the corpus callosum, internal capsules, corticospinal tracts, cerebellar white matter, and subcortical regions may become involved [6,7].

Several findings in the present case support the radiological consideration of MLD: the abnormalities were bilateral, highly symmetric, confluent, centered in the periventricular and deep white matter, and relatively spared the U-fibers. The reported onset of regression at approximately 18 months also overlaps with the late-infantile phenotype, in which gait disturbance and loss of motor abilities are common early manifestations [1,2]. Epilepsy can occur as the disease advances [2].

Some imaging features in this case were less typical. No definite tigroid pattern and no definite callosal signal abnormality were identified, and overt atrophy or extensive tract involvement was absent despite the reported duration of decline. These observations are a useful reminder that MRI appearances in MLD vary with disease stage and may be relatively mild or nonspecific; callosal involvement, for example, is a frequent but not universal early sign [8]. In the present patient, the diagnosis did not rest on imaging alone but was established biochemically, underscoring that MRI serves to raise suspicion and direct confirmatory analysis rather than to provide definitive proof.

The main acquired differential diagnosis initially considered was chronic perinatal white matter injury, because a history of fetal distress, early developmental delay, spasticity, and inability to walk can all be produced by a static hypoxic-ischemic insult. In this child, however, the neonatal course was largely reassuring, with prompt Apgar recovery, no documented hypoxic-ischemic encephalopathy, and normal neonatal cranial ultrasonography. Established periventricular leukomalacia typically demonstrates periventricular volume loss, ventriculomegaly with irregular contours, deep sulci approaching the ventricles, and variable atrophy [9,10]; these destructive features were not present, whereas the white matter signal abnormality was strikingly symmetric and confluent. The benign perinatal history and the biochemical results together make a purely perinatal explanation untenable.

Clinical evolution is therefore decisive. Cerebral palsy is attributed to a non-progressive disturbance of the developing brain [4]. Motor function can change with growth, orthopedic complications, intercurrent illness, or epilepsy, but a true loss of previously acquired developmental skills should not automatically be attributed to cerebral palsy. In the present patient, objective documentation of which milestones were acquired and subsequently lost would strengthen the distinction between progressive regression and severe early developmental impairment.

Confirmation of MLD requires more than reduced arylsulfatase A activity alone, because pseudodeficiency alleles can lower measured enzyme activity without causing disease. The demonstration of increased urinary sulfatide excretion in this patient, in addition to low enzyme activity, addresses this pitfall and supports genuine enzyme deficiency [3]. When clinical and biochemical findings are discordant, additional testing—including molecular analysis of ARSA and consideration of saposin B deficiency—may be required, and peripheral nerve conduction studies can provide supportive evidence of a demyelinating neuropathy [3]. Molecular characterization, although not performed here, remains valuable for genetic counseling and prenatal diagnosis in future pregnancies.

This report remains limited by the absence of molecular confirmation, standardized developmental assessment, electrophysiological testing, serial imaging, and long-term follow-up. Nonetheless, the concordance of a characteristic clinical course, a suggestive MRI pattern, reduced arylsulfatase A activity, and elevated urinary sulfatides supports a confident diagnosis of MLD. The principal value of the case lies in illustrating how a symmetric confluent white matter pattern and a history of regression can redirect the evaluation of a child previously labeled as having cerebral palsy toward an inherited, progressive white matter disorder and its appropriate confirmatory work-up.

Conclusion

Bilateral, symmetric periventricular and deep white matter abnormalities with relative sparing of the subcortical U-fibers are suggestive of a leukodystrophy and should raise particular concern for MLD. In a child with a perinatal risk history, imaging findings must be interpreted alongside the neonatal course and clinical evolution; here, a reassuring neonatal history and, above all, documented developmental regression argued against a static cerebral palsy phenotype and prompted confirmatory testing. Reduced arylsulfatase A activity with increased urinary sulfatide excretion established the diagnosis of metachromatic leukodystrophy. MRI should guide, but not replace, biochemical confirmation, and developmental regression in a child labeled as having cerebral palsy warrants renewed diagnostic evaluation.

Consent

Written informed consent for publication of this case and the anonymized images was obtained from the child's legal guardians.

Conflict of Interest

The authors declare no conflict of interest.

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