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# Redefining the Pediatric Phenotype of X-Linked Monocarboxylate Transporter 8 (MCT8) Deficiency: Implications for Diagnosis and Therapies

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## Abstract

X-linked monocarboxylate transporter 8 (MCT8) deficiency results from a loss-of-function mutation in the monocarboxylate transporter 8 gene, located on chromosome Xq13.2 (Allan-Herndon-Dudley syndrome). Affected boys present early in life with neurodevelopment delays but have pleasant dispositions and commonly have elevated serum triiodothyronine. They also have marked axial hypotonia and quadriparesis but surprisingly little spasticity early in their disease course. They do, however, have subtle involuntary movements, most often dystonia. The combination of hypotonia and dystonia presents a neurorehabilitation challenge and explains why spasticity-directed therapies have commonly produced suboptimal responses. Our aim was to better define the spectrum of motor disability and to elucidate the neuroanatomic basis of the motor impairments seen in MCT8 deficiency using clinical observation and brain magnetic resonance imaging (MRI) in a cohort of 6 affected pediatric patients. Our findings identified potential imaging biomarkers and suggest that rehabilitation efforts targeting dystonia may be more beneficial than those targeting spasticity in the prepubertal pediatric MCT8 deficiency population.

## Keywords

monocarboxylate transporter 8 deficiency, dystonia, magnetic resonance imaging, white matter tract, diffusion tensor imaging

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Sixty years after the initial report by Allan et al[1] in 1944, Dumitrescu et al[2] and Friesema et al[3] independently reported an association between the male Allan-Herndon-Dudley syndrome phenotype, abnormal thyroid function studies (typically elevated triiodothyronine and mildly decreased thyroxine levels), and loss-of-function mutations in the thyroid hormone cell-membrane transporter gene, monocarboxylate transporter 8, located on chromosome Xq13.2.[3,4] Monocarboxylate transporter 8 is expressed in numerous human tissues, including brain, skeletal muscle, heart, lung, and kidney. Males with loss-of-function mutations in this transporter present in early childhood with moderate-to-severe psychomotor impairment; absent or limited dysarthric speech; and attentive, affable dispositions.[4] The clinical course is characterized by persistent axial hypotonia and quadriparesis, with hyperkinetic movements (dystonia, choreoathetosis) in early childhood and gradual onset of spasticity in later childhood and adulthood. Most children have decreased weight for height, often in association with generalized muscle hypoplasia.[4,5] Brain magnetic resonance imaging (MRI) can be normal in very young infants, but there is typically evidence of delayed myelination or hypomyelination in infants 12 months and older.[4,6] The MCT8 gene abnormality can be easily identifiable by single gene sequencing or multiple ligation probe amplification (MLPA) analysis.[7-10]

In contrast to typical patients with early spastic quadriparetic cerebral palsy, boys with monocarboxylate transporter 8 deficiency have little to no spasticity with subtle involuntary movements at onset mimicking spasticity and therefore present

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**Table 1.** Distribution of Magnetic Resonance Imaging (MRI) Sequences per Patient (X = Present), Number of MRIs per Patient, and the Age of the Patient During the Study.

| Patient | T1WI | T2WI | FLAIR | Vol. T1W | Spectroscopy[a] | DTI | No. of MRIs | Age at time of MRIs |
|---|---|---|---|---|---|---|---|---|
| 1 | X | X | X | X | X | X | 4 | 8 mo, 4 y, 6 y, 7y |
| 2 | X | X | X | X | X | X | 2 | 3 y, 5 y |
| 3 | X | X | X | X | X | X | 2 | 3 y, 5 y |
| 4 | X | X | X | | X | | 2 | 5 mo (MRS only), 1 y |
| 5 | X | X | X | X | X | | 2 | 5 mo, 2 y |
| 6 | X | X | | | | | 1 | 2 y |

Abbreviations: DTI, diffusion tensor imaging; FLAIR, fluid-attenuated inversion recovery; MRS, magnetic resonance spectroscopy; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; Vol. T1W, volumetric acquired T1-weighted imaging.
[a]MRI spectroscopy, single voxel.

a unique challenge to standard early intervention/rehabilitation needs. Failure to accurately characterize their movement disorders may lead to misguided use of antispasmodic medications as well as other spasticity-directed interventions, resulting in suboptimal treatment results.

In order to create more effective and tailored treatment strategies for young boys with monocarboxylate transporter 8 deficiency for both the short and long term, we set out to closely investigate the early clinical and neuroanatomic spectrum of motor disabilities in a cohort of 6 prepubertal MCT8-deficient patients through clinical and imaging assessments.

## Methods

A small, multinational cohort of 6 patients, aged 5 months to 7 years, with documented pathogenetic X-linked monocarboxylate transporter 8 gene abnormalities had direct and/or indirect (video-based) pediatric neurologic evaluations performed by 2 of the authors (KRH, RKL). All of the patients had brain MRIs performed under anesthesia in their respective countries and then analyzed by 2 of the authors (MGM and LB, neuroradiologist and clinical research neurologist, respectively). Five of the 6 participants had multiple brain MRI scans. The authors had the parents' consent to analyze the data. Although multinational, the authors followed the ethical principles of the Declaration of Helsinki in conducting this pilot study. In 3 cases, the authors were able to compare brain MRIs from the study subjects to those of normal controls. The deidentified normal comparison images were obtained from 2 age-matched subjects who had had brain MRIs performed at the Medical University of South Carolina for other indications (headache and possible febrile seizure, respectively). The use of these comparison images were approved by the university's institutional review board. The brain MRI images were assessed with special attention to the white matter tracts, basal ganglia, and cerebellum.

## Results

Neurologic evaluations were performed (and/or reviewed in video format) on this previously genetically diagnosed cohort of X-linked monocarboxylate transporter 8 deficiency patients. Normocephaly was commonplace and happy disposition best described their behavior in association with multiple neurodevelopmental disabilities. Assessment of the motor examinations revealed a common pattern of hypotonic quadriparesis with superimposed hyperkinetic movements, predominantly dystonia but also included chorea and athetosis. Global hypotonia and poor head control were historically present from early in the disease course and persisted even in the older patients in our study cohort. The children appeared active, attentive, and nonverbal but very alert to visual stimuli. The patients commonly demonstrated frequent episodes of mild to moderate dystonic movements and hypertonic posturing of the upper extremities > lower extremities, frequently triggered by emotions, stressful conditions, or sensory stimuli. Early signs of lower extremity hyperreflexia and mild tightening of the heel cords with positive Babinski reflexes usually present by about 3 years of age. These motor findings only very slowly progressed, primarily in the lower extremities, while the upper extremities and neck muscles were primarily affected by the progression of the movement disorders. Otherwise, the striking progressive generalized hypoplasia of child's general musculature and persistent hypotonia were noteworthy.

Thirteen brain MRI studies were obtained and assessed. One patient had 4 MRIs, 4 patients had 2, and 1 patient had only 1 MRI study. The imaging protocols were heterogeneous. The following imaging sequences were present: T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery, volumetric T1-weighted imaging, spectroscopy, and diffusion tensor imaging. Not all sequences were performed on every patient. Table 1 illustrates the age and imaging sequence distribution of the brain MRI studies over time. Although the MRI studies had distinct and heterogeneous protocols, the images were all of good diagnostic quality.

Brain MRI assessment revealed normal macromorphology of the supra- and infratentorial structures in all subjects. Delayed myelination was observed in all subjects. By 8 months of age, delayed myelination was visible, although subtle. The abnormal myelination pattern became more conspicuous over time, primarily with involvement of distinct supratentorial white matter tracts (Figure 1). The myelination of the corpus callosum and cortical spinal tracts (seen in the internal capsule) progressed, but the myelination of the subcortical U-fibers and periventricular white matter remained inadequate, probably because of hypomyelination or dysmyelination. Increased T2-weighted signal was most pronounced in the subcortical white matter but was also present in the supratentorial periventricular white matter, most likely due to myelination abnormalities

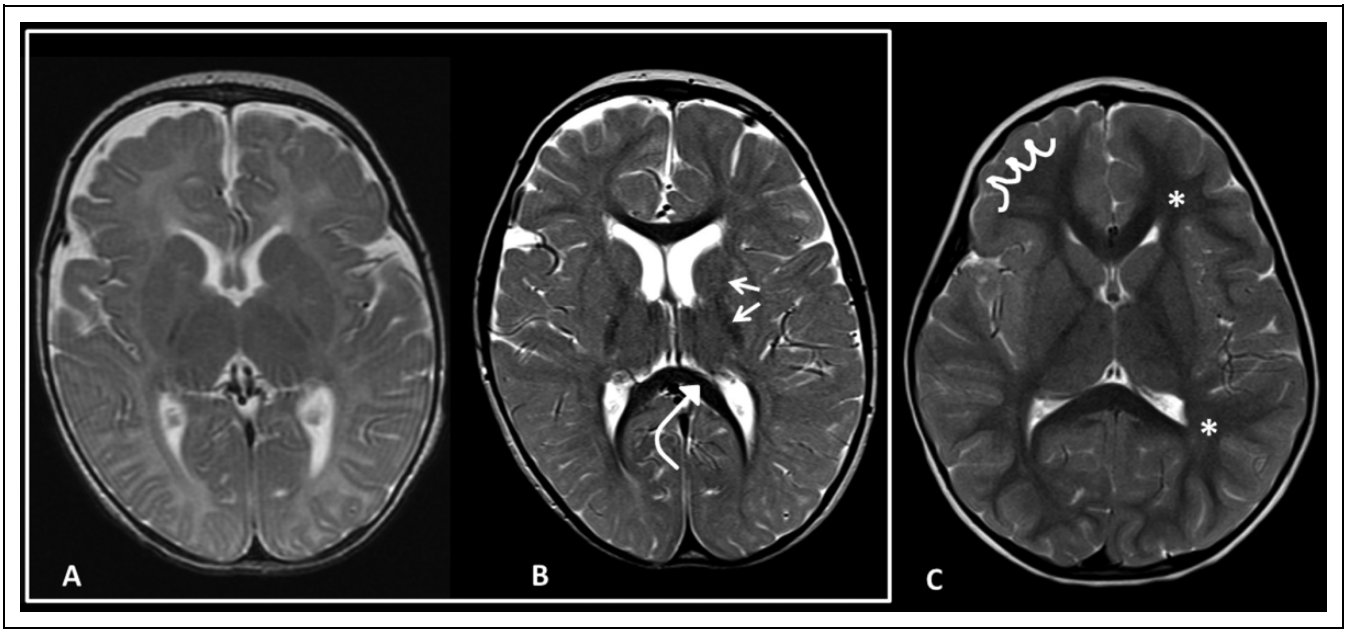


**Figure 1.** T2-weighted MRI images from Patient 1 with X-linked monocarboxylate transporter 8 deficiency at 8 months of age (A) and 6 years of age (B) in comparison to a normal 6-year-old control patient (C). Note that corpus callosum (curved arrow) and cortical spinal tracts (arrows) show progressive myelination and almost normal appearance when compared to control. The (*) and curved lines on (C) show the normal pattern of the white matter and U-fiber, which are poorly defined in X-linked monocarboxylate transporter 8 deficiency (B).

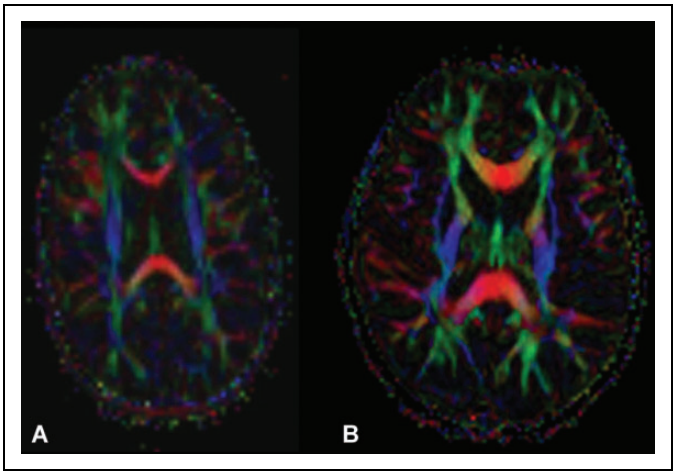


**Figure 2.** Shows tractographic images from an X-linked monocarboxylate transporter 8 deficiency patient at 5 years of age (A) and a control subject (B). Note that the anteroposterior directed tracts (green) are poorly defined in the X-linked monocarboxylate transporter 8 deficiency patient (A) when compared to control (B). The corpus callosum (red fibers) and cortical spinal tracts (blue fibers) appear better defined and similar in appearance in both images.

and/or gliosis. Three patients had diffusion tensor imaging sequences, and in all 3 cases, the supratentorial white matter tracts were poorly defined relative to those of the normal controls. This lack of definition was most conspicuous in the anteroposteriorly directed association tracts (green tracts on Figure 2). By contrast, the commissural white matter tracts (corpus callosum) and corticospinal tracts (red and blue tracts, respectively, on Figure 2) were almost normal in appearance.

## Discussion

Although Allan et al[1] first reported the phenotype of what is now known as monocarboxylate transporter 8 deficiency,[2,3] a number of small case series in pediatric and adult subjects have been instrumental in expanding and refining the phenotypic spectrum of this disorder.[1-6,11] The early core motor features of the disease include hypotonia and muscular hypoplasia in all cases; hyperkinetic movements, including dystonia and choreoathetosis, in early childhood in a large majority of cases; and spasticity that slowly evolves with advancing age in many cases.[1-4,11-13]

The motor phenotype of monocarboxylate transporter 8 deficiency presents a unique challenge to standard early intervention and rehabilitation strategies. In our experience, frequently applied spasticity-directed therapies produce suboptimal results. Our findings suggest that early in the disease course, monocarboxylate transporter 8 deficiency should be conceived of not as a neurodevelopmental disability with hypotonia and a strong *spastic* component, but rather as a neurodevelopmental disability with hypotonia and a strong *dystonic* component, which may be followed by significant spasticity only as the individual ages.

Many involuntary movement disorders stem from abnormalities in the basal ganglia, the cerebellum, or the white matter tracts that connect the 2 structures with cortical centers. In our monocarboxylate transporter 8 deficiency group, the cerebral cortex, cerebellum, and basal ganglia showed normal macromorphology in all subjects. However, in the past 25 years there have been large advances in neuroimaging related to movement disorders. Functional brain MRIs and studies of white matter

connectivity have led to novel insights regarding the pathogenesis of movement disorders. Recent reports of MRI diffusion tensor imaging in patients with hereditary dystonia have revealed abnormalities of the white matter tracts,[14,15] sometimes in genotype-specific patterns.[16]

Conventional T1- and T2-weighted brain MRI sequences in our MCT8 cohort revealed hypomyelination that involved the subcortical U-fibers and periventricular white matter tracts that became more conspicuous over time in all 6 of our patients. By contrast, the callosal and cortical spinal tracts showed near-normal myelination. Diffusion tensor imaging, performed in 3 of our monocarboxylate transporter 8 deficiency patients, showed poor definition of the white matter association tracts with respect to normal controls, suggesting the presence of subtle microstructural abnormalities. The same 3 subjects had a normal-appearing corpus callosum. These findings are consistent with the presence of dystonia in our monocarboxylate transporter 8 deficiency study group.

This study has intrinsic limitations that must be considered. It is a retrospective, noncontrolled, pilot study of monocarboxylate transporter 8 deficiency patients with heterogeneous imaging data. The lack of well-controlled imaging data and the small number of subjects do not allow quantification of the white matter tracts with diffusion tensor imaging. Nevertheless, the clinical and brain MRI findings from this small, multinational cohort allow us to speculate that studying white matter tracts in larger populations of monocarboxylate transporter 8 deficiency patients and matched controls would likely clarify the aberrant connectivity patterns that produce the predominant motor phenotype in monocarboxylate transporter 8 deficiency. Although this pediatric cohort offers valuable information about the early motor impairments in X-linked monocarboxylate transporter 8 deficiency, it also should be noted that our results may not be applicable to the adult monocarboxylate transporter 8 deficiency population, because spasticity usually becomes a more prominent feature of the disorder over time. It is our hope that further longitudinal studies will lead to the identification of definitive connectivity biomarkers, which, in turn, will improve our ability to develop disease-specific treatments and neurorehabilitation strategies as well as monitor the effects of those therapies on the monocarboxylate transporter 8 deficiency patient's phenotype over time.

## Conclusion

Our group of X-linked monocarboxylate transporter 8 deficiency patients manifested a common pediatric neurologic phenotype, which was characterized by neurodevelopmental delays/intellectual disability; infantile hypotonia with muscular hypoplasia; and primarily the movement disorder dystonia, as opposed to spasticity. We expect that our results will help medical providers to recognize and screen for X-linked monocarboxylate transporter 8 deficiency in the pediatric population and to rethink the current neurorehabilitation approaches, which are dominated by therapies to address spasticity. Because MRI techniques suggest that there is a disruption of white matter tracts in this disorder, future imaging studies of white matter connectivity may yield biomarkers for any medical/rehabilitation therapies that are being studied.

### Author Contributions

Dr. Maria Gisele Matheus and Dr. Kenton R. Holden contributed to conception of the pilot study, data acquisition and interpretation, article drafting, and final approval. Dr. Rebecca K. Lehman and Dr. Leonardo Bonilha contributed to conception of the study, data interpretation, critical revision, and final approval of the article.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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### Ethical Approval

The authors had the parents' consent to analyze the data. Although multi-national, the authors followed the ethical principles of the Declaration of Helsinki in conducting this pilot study. In three cases, the authors were able to compare brain MRIs from the study subjects to those of normal controls. The de-identified normal comparison images were obtained from two age-matched subjects. The use of these comparison images were approved by the university's institutional review board.

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