DARS-associated leukoencephalopathy can mimic a steroid-responsive neuroinflammatory disorder

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ABSTRACT

Objective: To describe the expanding clinical spectrum of a recently described hereditary leukoencephalopathy, hypomyelination with brainstem and spinal cord involvement and leg spasticity, which is caused by mutations in the aspartyl tRNA-synthetase encoding gene *DARS*, including patients with an adolescent onset.

Methods: Three patients with mutations in *DARS* were identified by combining MRI pattern recognition and genetic analysis.

Results: One patient had the typical infantile presentation, but 2 patients with onset in late adolescence had a disease mimicking an acquired inflammatory CNS disorder. Adolescent-onset patients presented with subacute spastic paraplegia and had positive response to steroids. They had only minor focal supratentorial white matter abnormalities, but identical spinal cord changes involving dorsal columns and corticospinal tracts. Clinical presentation included subacute spastic paraplegia with partial improvement on steroids.

Conclusions: Focal T2 hyperintense white matter changes on brain MRI in combination with spinal cord signal abnormalities usually suggest acquired inflammatory conditions such as multiple sclerosis, especially in the context of relapsing course and a positive response to steroid treatment. Adolescents with mutations in *DARS* can present with a comparable clinical picture, broadening the clinical spectrum of hypomyelination with brainstem and spinal cord involvement and leg spasticity. ***Neurology*® 2015;84:226–230**

GLOSSARY

AspRS = aspartyl tRNA synthetase; **HBSL** = hypomyelination with brainstem and spinal cord abnormalities and leg spasticity; **LBSL** = leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate; **MS** = multiple sclerosis; **WES** = whole-exome sequencing.

Hypomyelination with brainstem and spinal cord abnormalities and leg spasticity (HBSL, OMIM 615281) is an inherited white matter disorder caused by autosomal recessive mutations in *DARS*, encoding the cytosolic aspartyl tRNA synthetase (AspRS).[1] HBSL was first described in 10 patients, all of whom had a severe presentation with infantile onset and extensive MRI signal abnormalities of the supratentorial white matter suggesting hypomyelination, as well as signal changes in the spinal cord. HBSL affects the same tracts as leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate (LBSL),[1] a disease caused by mutations in *DARS2*, encoding the mitochondrial counterpart of AspRS.[2,3]

Since the original publication, we identified 3 more patients, one with typical infantile onset and 2 young adults with disease onset in late adolescence, both with focal cerebral white matter

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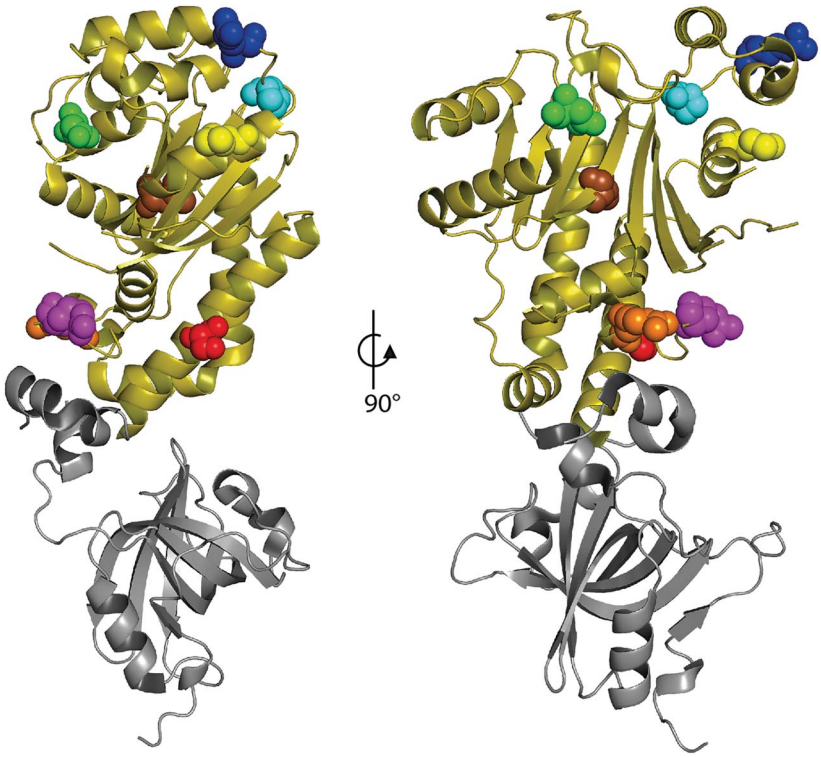
Figure 1 Positioning of *DARS* mutations in individuals with hypomyelination with brainstem and spinal cord abnormalities and leg spasticity



The images show the crystal structure of human aspartyl tRNA synthetase (AspRS) protein (PDB:4J15) including the catalytic domain (olive), and the hinge and the anticoding binding domains (gray). All hypomyelination with brainstem and spinal cord abnormalities and leg spasticity–associated variants (spheres) identified to date are located within the catalytic domain: p.Ser200 (red), p.Leu426 (brown), and p.Asp367 (green) (this publication); p.Met256 (red), p.Arg460 (blue), p.Pro464 (cyan), p.Arg487 (orange), and p.Arg494 (magenta).[1] The residues p.Ala274, p.Ser277, and p.His280 are not shown as they reside in a 9-residue loop that is disordered and therefore missing from this structure. The loop is known to be dynamic until docked with its cognate tRNA.[9]

abnormalities, spinal cord signal abnormalities, subacute disease onset, and partial steroid responsiveness, mimicking a neuroinflammatory disease.

METHODS Patients were identified from the databases of the Center for Children with White Matter Disorders, VU University Medical Center, Amsterdam, the Netherlands; The Undiagnosed Diseases Program at the NIH, Bethesda, Maryland; and the Department of Neurology, Children's National Medical Center, Washington, DC. Brain and spinal cord MRIs were analyzed using MRI pattern recognition.[4,5] *DARS* sequencing was performed as described previously.[1]

Standard protocol approvals, registrations, and patient consents. The institutional review boards of these institutions approved this study, and appropriate informed consent was obtained.

RESULTS **Clinical presentation.** Patient 1 developed normally until the age of 14 months, when, after a brief viral illness, she became irritable and lost several words and the ability to sit without support. She subsequently developed nystagmus and leg spasticity. She showed striking improvement in axial muscle tone and strength after oral ibuprofen treatment initiated for discomfort at teething. Steroids were without additional beneficial effect. She continued to make slow progress and learned to walk with support. Her cognitive abilities were above average.

Patient 2 is a 22-year-old man who was involved in a traffic accident at age 18, resulting in brief loss of consciousness and a small subdural bleed. He recovered completely within 2 days. One month later, he presented with progressive weakness of his legs more than his arms. He experienced rapid deterioration and lost the ability to walk without support in the course of 3 months. Neurologic examination revealed ataxia, leg spasticity, diffuse hyperreflexia with bilateral extensor plantar responses, and distal decrease in position and vibration sense of both legs. There were no oligoclonal bands present in CSF. He received one course of IV steroids (1,000 mg methylprednisolone per day for 5 days) and thereafter gradually regained the ability to ambulate within 1 year. Two years later, he had mild residual leg spasticity.

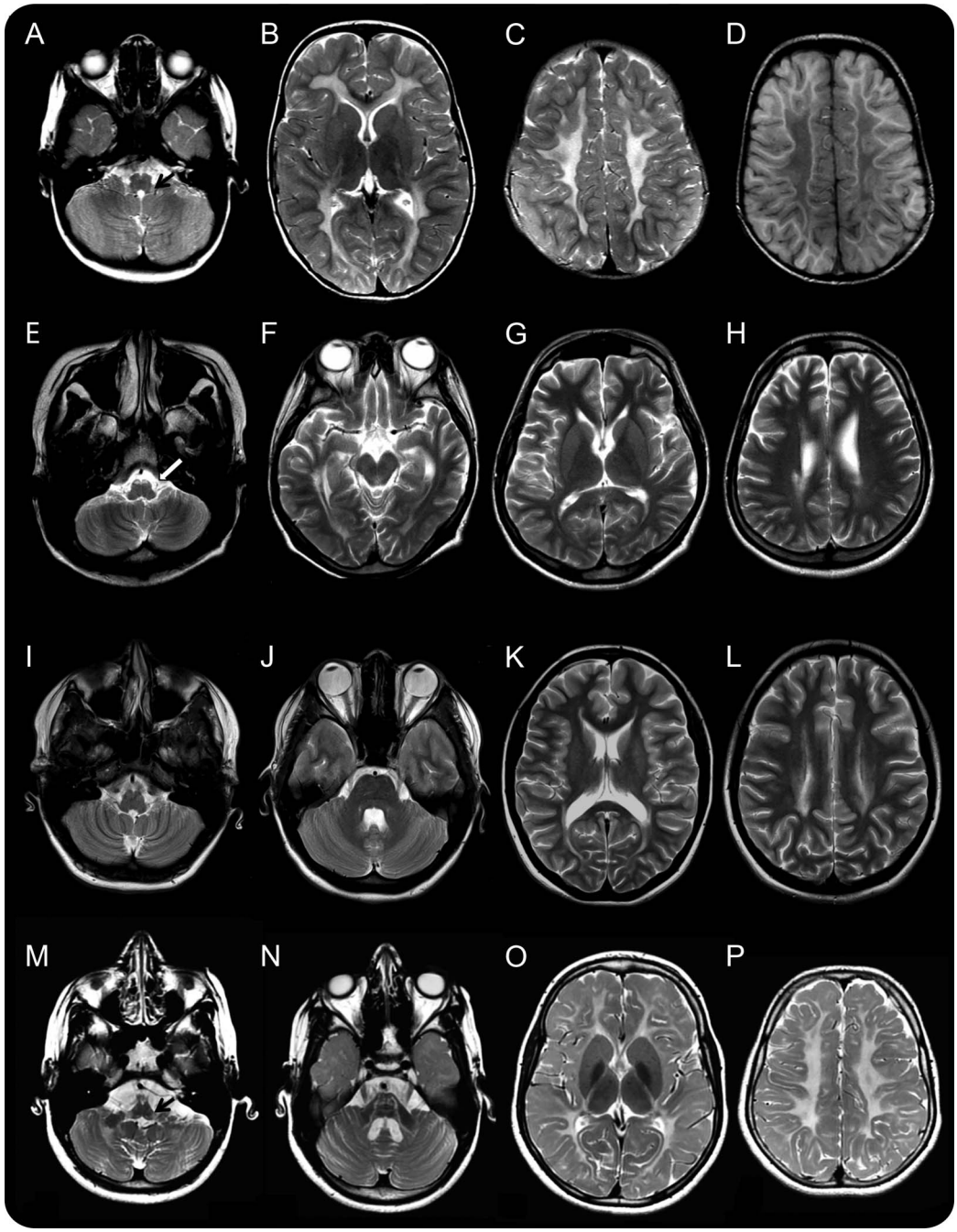
Patient 3 is a 20-year-old woman who developed progressive leg spasticity and urinary urgency and frequency from the age of 16 years. There were no oligoclonal bands present in CSF. Initially, a neuroinflammatory condition such as multiple sclerosis (MS) was suspected and she received steroid pulse treatments every 3 to 6 months (1,000 mg methylprednisolone per day for 3 days). Her symptoms would improve within days, but then slowly reemerge over months until the next treatment was administered. The possibility of hereditary spastic paraplegia was considered in view of signal changes in the long tracts over the entire length of the spinal cord. Whole-exome sequencing (WES) was performed to ascertain the molecular basis of her disease.

***DARS* mutations.** In patients 1 and 2, the original suspicion was LBSL, but we detected no pathogenic *DARS2* mutations. Mutations in *DARS* were detected subsequently by Sanger sequencing. The *DARS* mutation in patient 3 was identified by WES.

Patient 1 was compound heterozygous for c.599C>G; p.Ser200Cys and c.830C>T; p.Ser277Phe. Patient 2 was homozygous for c.1277T>C; p.Leu426Ser, and patient 3 compound heterozygous for c.839A>T; p.His280Leu and c.1099G>C; p.Asp367His (figure 1).

MRI abnormalities. Brain MRI of the patient with infantile onset showed homogeneous T2 hyperintensity of the supratentorial white matter with sparing of the U-fibers. This T2 hyperintensity was more pronounced than usually seen in other children with HSBL. In contrast, in the 2 patients with adolescent onset, brain MRI showed only limited, focal areas of

Figure 2 Brain MRI



Brain MRI in patients with infantile and adult onset. (First row) Patient 1, age 2 years. Hyperintense T2 signal of the inferior cerebellar peduncles (A; arrow) and the supratentorial white matter sparing the U fibers (B, C). Corresponding hypointense T1 signal of the centrum semiovale, again with sparing of the U fibers (D). (Second row) MRI of patient 2, age 19 years. (E) Hyperintense T2 signal of the pyramids in the medulla oblongata (white arrow). (F-H) Focal periventricular signal changes with hyperintense T2 signal; myelination is normal. (Third row) Patient 3, age 18 years, without changes in brainstem or cerebellar white matter (I, J). The patient has focal periventricular hyperintense T2 signal changes (K, L). (Fourth row) For comparison, a patient aged 9 years with classic hypomyelination with brainstem and spinal cord abnormalities and leg spasticity and characteristic MRI abnormalities (patient 4 from Taft et al.,[1] 2013) shows signal abnormalities of the brainstem, including corticospinal tracts, medial lemniscus, and inferior (arrow) and superior cerebellar peduncles (M, N) and diffuse hyperintense T2 signal of the entire supratentorial white matter typical of hypomyelination (O, P) also involving the U fibers.

T2 hyperintensity in the periventricular region. Myelination was normal (figure 2). There was no contrast enhancement.

Spinal cord imaging in all patients showed abnormal T2 hyperintense signal of the dorsal columns (nonhomogeneously in patient 3) and the lateral

corticospinal tracts. Patient 2 additionally showed prominent involvement of the anterior corticospinal tracts (figure 3).

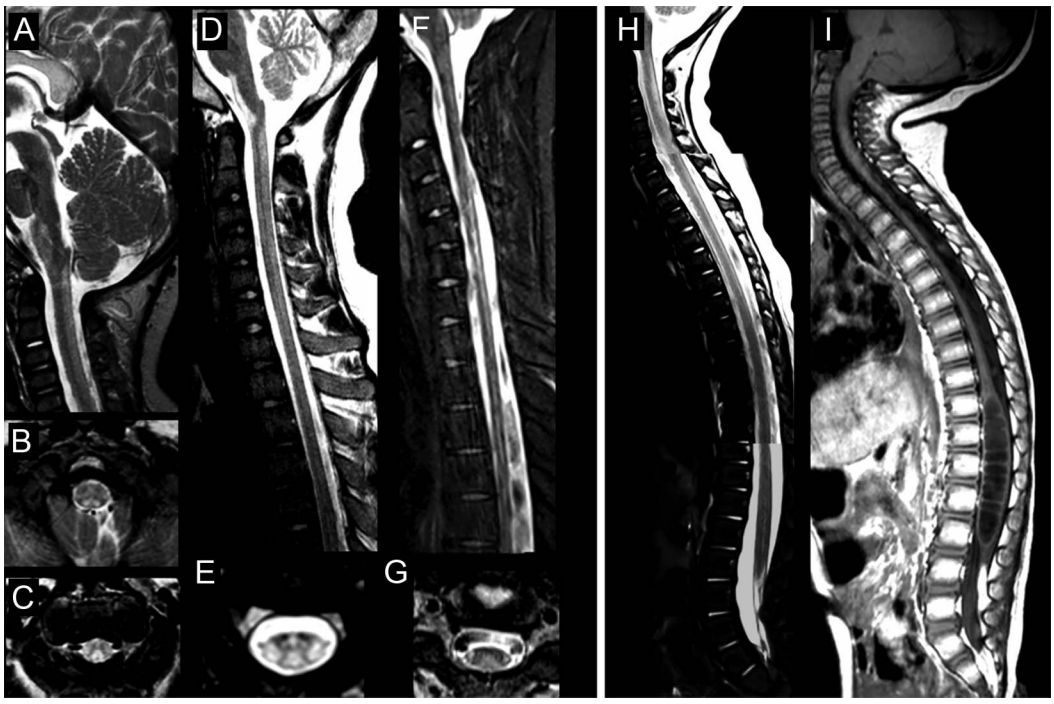
DISCUSSION HBSL was initially described as an infantile onset disease.[1] Identification of adult patients with presentation in late adolescence and only focal white matter changes on brain MRI extends the disease spectrum beyond the infantile phenotype. All patients identified so far carried missense mutations leading to amino acid changes in the catalytic domain of AspRS.

Several patients with the classical form of HBSL —patient 1 in this study, and 2 out of 10 patients in the original series[1]—showed regression after mild viral illness or vaccination. The 2 patients with adolescent onset showed subacute deterioration. In 4 patients (patients 2 and 3 in this study and 2 patients from the original description), administration of steroids was followed by clinical improvement and was assumed to be responsible for the partial recovery these patients experienced. The relapsing-remitting clinical course, response to steroids, and combination of focal white matter and spinal cord signal changes would usually suggest an inflammatory demyelinating disorder such as MS or neuromyelitis optica. Thus, HBSL should be included in the differential diagnosis of CNS inflammatory disorders. A clue to HBSL is the selective involvement of specific spinal tracts over the entire length of the spinal cord, which argues against a primary inflammatory CNS disease.

Notably, 2 children from the original study had an additional spinal cord abnormality, namely tethering.[1] The current number of patients is too small to determine if this is a chance association, but a tethered cord might be another feature of *DARS* mutations. Patients with HBSL should be investigated with spinal imaging to detect this complication.

LBSL and HBSL show some striking similarities,[1] but also differences. The typical clinical course in LBSL is slowly progressive, although 2 patients with sudden deterioration after a mild head trauma followed by fever have been reported.[6] Infantile onset with severe disease course is rare in LBSL. MRI in these cases shows diffuse supratentorial white matter abnormalities, reminiscent of those seen in HBSL,[7,8] whereas in most LBSL cases, supratentorial signal changes are focal.[2,8] The intraparenchymal trajectories of the trigeminal nerves and mesencephalic trigeminal tracts are typically affected in LBSL,[2] but normal in HBSL.[1] Still, the finding of a mild adult phenotype of HBSL with only focal brain white matter abnormalities and spinal cord changes similar to those seen in LBSL reinforces the possibility that there may be a common pathogenic mechanism. Intriguingly, recent

Figure 3 Spinal cord MRI



Findings on spinal cord MRI. (A–C) Patient 1, abnormal signal of dorsal columns and lateral corticospinal tracts. (D, E) Patient 2, abnormal signal of dorsal columns and anterior and lateral corticospinal tracts. (F, G) Patient 3, signal changes in dorsal columns and lateral corticospinal tracts. For comparison, 2 previously described patients[1] are shown with the typical signal changes, as well as tethering (H, I) and syringomyelia (I).

structural data have demonstrated a similar 3D structure of both cytosolic and mitochondrial AspRS despite poor sequence homology of their respective genes, raising the possibility of functional overlap in situ, which might provide clues to the striking parallels between LBSL and HBSL.[9]

Cytosolic AspRS is part of the multisynthetase complex,[10] which appears to play an important role not only in tRNA synthesis, but also in multiple cellular processes, including cytokine and immune responses.[11] The apparent positive response of several patients with HBSL to anti-inflammatory treatment might be related to these alternative functions. Therefore, treatment with steroid pulse therapy might be considered in HBSL, especially in the case of (sub) acute deterioration. Careful determination of clinical outcome goals and treatment duration needs to be individualized for each patient.

AUTHOR CONTRIBUTIONS

Nicole I. Wolf coordinated this study and wrote the first draft of the article. Camilo Toro performed WES, identified *DARS* mutations in one patient, and reviewed the article. Ilya Kister contributed patient and MRI data and reviewed the article. Kartikasalwah Abd Latif contributed patient and MRI data and reviewed the article. Richard Leventer contributed patient and MRI data and reviewed the article. Amy Pizzino contributed patient data. Cas Simons analyzed mutation data and reviewed the article. Truus E.M. Abbink performed molecular analysis of the *DARS* gene and reviewed the article. Ryan J. Taft analyzed mutation data and reviewed the article. Marjo S. van der Knaap identified patients and reviewed the article. Adeline Vanderver contributed patient and MRI data and reviewed the article.

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