Hypomyelination and Congenital Cataract

Broadening the Clinical Phenotype

Roberta Biancheri, MD, PhD; Federico Zara, PhD; Andrea Rossi, MD; Mikael Mathot, MD; Marie Cecile Nassogne, MD; Cengiz Yalcinkaya, MD; Ozdem Erturk, MD; Behyan Tuysuz, MD; Maja Di Rocco, MD; Elisabetta Gazzero, MD; Marianna Bugiani, MD; Resie van Spaendonk, MD; Erik A. Sistermans, MD; Carlo Minetti, MD; Marjo S. van der Knaap, MD, PhD; Nicole I. Wolf, MD, PhD

Objective: To further delineate the clinical spectrum of hypomyelination and congenital cataract (HCC), a rare autosomal recessive white matter disorder due to deficiency of a membrane protein, hyccin, encoded by FAM126A.

Design: Case reports and literature review.

Setting: University hospital.

Patients: Nine additional patients with HCC.

Results: Cataract was congenital in 5 patients; it was found at 4, 5, and 7 months in 3 patients, and only a mild lens opacity was noted at age 3 years in the remaining patient. Neurologic presentation was at birth in 1 child, was characterized by developmental delay at the end of the first year of life in 7 patients, and was characterized by sudden motor regression in the second year of life in the remaining patient. Three patients were able to walk with support only, 5 achieved the ability to walk without support, and the remaining patient was not able to stand at age 2 years. Mental retardation was present in all patients. Peripheral neuropathy was present in the 8 patients who underwent neurophysiological investigations. Brain magnetic resonance imaging showed hypomyelination associated with periventricular white matter abnormalities in all patients and brainstem pyramidal tract involvement in 8. Molecular analysis depicted 3 novel mutations and the previously reported IVS5+1G>T mutation.

Conclusions: Our study broadens the clinical spectrum of HCC. The clinical variability ranges from severe early-onset neurologic impairment to a milder phenotype. In contrast to this clinical variability, the peculiar magnetic resonance pattern of hypomyelination combined with increased periventricular white matter water content allows distinction of HCC from other forms of hypomyelinating leukoencephalopathies.

Arch Neurol. 2011;68(9):1191-1194

Author Affiliations are listed at the end of this article.

We have identified 9 patients with HCC from 7 unrelated families, all of Mediterranean origin. In 6 families, the parents were consanguineous. Patients 7 and 8 are siblings; patient 9 is their first-degree cousin. Having received parental written informed consent, the investigations fulfilled our institutions' ethical rules for human studies.

Samples of DNA were obtained from peripheral lymphocytes using standard techniques. Mutational screening of FAM126A and marker genotyping were performed as previously described.1

Brain magnetic resonance imaging (MRI) was performed in all patients for a total of 15 examinations, consistently including axial and/or sagittal T1-weighted spin-echo and axial T2-weighted fast spin-echo images, whereas axial and/or coronal fluid-attenuated inversion recovery images were obtained in 11 examinations. Motor nerve conduction velocity studies were performed in 8 of 9 patients. Sural nerve biopsies were performed in 2 patients and were processed for light and electron microscopy with standard techniques.3
Clinical and laboratory findings are summarized in the following subsections. Details are provided in the eTable (http://www.archneurol.com).

CLINICAL AND NEUROPHYSIOLOGICAL FEATURES

All patients were born at term after an uneventful pregnancy. The perinatal history was normal in 8 of 9 patients; patient 2 showed hypotonia and feeding difficulties during the neonatal period. Five patients showed bilateral cataract at birth; in 3 patients, bilateral cataract was found between 3 and 7 months of life, and in patient 3, a mild opacity of the lens was diagnosed at 3 years of age. All patients except patient 3 underwent ocular surgery. Nystagmus developed in 6 of 9 patients, but no patient presented with congenital or early nystagmus. The early development was normal in all patients. Developmental delay was most often noted at the end of the first year of life: walking without support was achieved between ages 12 and 24 months in 5 of 9 patients (patient 3 suddenly lost this ability at age 20 months); 3 of 9 patients were able to walk with support between 12 and 18 months of age, whereas the remaining patient was not able to stand at 26 months of age. Most patients gradually lost the ability to walk, becoming wheelchair bound between ages 3 and 15 years. Slowly progressive scoliosis appeared concurrently with the loss of the ability to walk. Neurologic examination showed truncal hypotonia and pyramidal signs in 8 of 9 patients. Cerebellar signs, such as truncal titubation and intention tremor, were evident in 3 patients. Muscle weakness and wasting of the lower limbs, indicating peripheral nervous system involvement, were present in all patients. Mild mental retardation was also present in all patients. Only 1 patient experienced a few seizures. Motor nerve conduction velocity was decreased in all patients examined.

MOLECULAR FINDINGS

Molecular analysis showed 3 novel mutations in 5 patients (c.215_224dup, c.725del, and c.274delA) and the previously reported1 IVS5+1G>T mutation in 4 unrelated patients (eTable). Haplotype analysis of 3 of these patients and of 1 patient carrying the same mutation (described by Zara et al3) demonstrated the same haplotype in all of them (eFigure 1).

NEUROIMAGING AND NEUROPATHOLOGICAL STUDIES

In all patients, MRI signal behavior was consistent with the definition of hypomyelination on T1- and T2-weighted images (Figure 1 and Figure 2). In addition, we found evidence of additional periventricular abnormalities, with an anterior-to-posterior gradient of severity (Figures 1 and 2). These areas were characterized by even higher T2 signal intensity and associated with T1 hypointensity, suggesting an increased water content in the affected white matter. On follow-up studies, white matter atrophy was seen in the same regions, with enlargement of the lateral and third ventricles and thinning of the corpus callosum in the older patients. One patient had slight cerebellar atrophy.

The cerebellar white matter was mildly hyperintense on T2-weighted images and was close to the signal intensity of the adjacent cortical gray matter, resulting in a “blurred” gray matter/white matter interface at this level in 1 patient. Pyramidal tracts showed an abnormally high T2 signal in the mesencephalon and pons in 7 patients and in the mesencephalon only in 1 patient (eFigure 2). This hyperintensity seemed to improve with age in 2 of these patients. Sural nerve biopsy showed minimal changes, as illustrated in Figure 3.

COMMENT

Despite advances in the diagnosis of white matter disorders in children, almost half the patients remain without a definite diagnosis. Hypomyelination is the single largest category among white matter disorders of unknown origin, representing a major diagnostic challenge because the MRI changes are thought to be uniform and nonspecific. Distinctive clinical findings, such as cataract in HCC or hypodontia in the 4H syndrome (hypomyelination with hypogonadotropic hypogonadism and hypodontia), have been considered crucial for
making the diagnosis of specific entities. Subtle but consistent MRI abnormalities also help in differentiating hypomyelinating disorders.\(^8\)

In the original description of HCC,\(^1,2\) bilateral congenital cataract was considered to be a major finding, and the neurologic picture was stereotyped: developmental delay was noticed at the end of the first year of life, the ability to walk was achieved during the second year with support only, and patients became wheelchair bound at the end of the first decade. In contrast, in the present study, cataract was not invariably congenital, and only a mild lens opacity was diagnosed in the third year of life in 1 patient. Furthermore, the age at neurologic presentation and the severity of the neurologic impairment varied. Indeed, 5 patients showed a milder phenotype, being able to walk without support, and 1 child developed normally until a sudden motor regression occurred during the second year of life. However, at the other end of the clinical spectrum, 1 patient showed hypotonia and feeding difficulties in the neonatal period, early-onset developmental delay, and wheelchair dependency from age 3 years. The patient with the most severe clinical picture and the one with the mildest phenotype carried the same mutation (IVS5 + 1G>T) reported in 6 other patients (including another of this series), with the typical occurrence of congenital/early-onset cataract and the classic neurologic presentation and outcome. The significant clinical variability is likely due to modifiers from the genetic background of each patient. Genotyping of highly polymorphic microsatellite markers covering the HCC locus in 4 unrelated patients with this mutation revealed the presence of a common haplotype spanning approximately 340 kilobases, suggesting a founder effect. The identification of additional patients will eventually determine whether this effect is restricted to individuals of Mediterranean descent. Late-onset cataract has been reported\(^9\) in a Turkish family with a homozygous, large intragenic deletion encompassing 2 exons of the FAM126A gene. In one child, bilateral cataract developed at 9 years of age; in another, unilateral cataract developed at 12 years of age.

In conclusion, the clinical variability of HCC is greater than previously described, but the MRI features of hypomyelination combined with increased periventricular white matter water content are consistently observed, distinguishing HCC from other forms of hypomyelinating leukoencephalopathies. In addition, most of our patients showed increased T2 signal of the pyramidal tracts in the mesencephalon and pons. Thus, even in the absence of cataracts or with atypical clinical findings, these characteristic MRI findings suggest the diagnosis of HCC, and mutation analysis of FAM126A should be the first diagnostic step.

Accepted for Publication: November 17, 2010.

Author Affiliations: Department of Neuroscience (Drs Biancheri, Zara, Gazzero, and Minetti), Pediatric Neuroradiology (Dr Rossi), and Second Unit of Pediatrics (Dr Di Rocco), G. Gaslini Institute, Genova, Italy; Service de Neurologie Pédiatrique, Cliniques universitaires Saint-...
Luc, Université catholique de Louvain, Bruxelles, Belgium (Drs Mathot and Nassogne); Division of Child Neurology, Department of Neurology (Drs Yalcinkaya and Erturk), and Department of Pediatric Genetics (Dr Tuysuz), Istanbul University Cerrahpasa Faculty of Medicine, Istanbul, Turkey; and Departments of Pathology (Dr Bugiani), Clinical Genetics (Drs van Spaendonk and Sistermans), and Child Neurology (Dr van der Knaap and Wolf), VU University Medical Center, Amsterdam, the Netherlands.

Correspondence: Roberta Biancheri, MD, PhD, Department of Neuroscience, G. Gaslini Institute, Largo G. Gaslini 5, 16147 Genova, Italy (roberta@biancheri.com).

Author Contributions: Study concept and design: Biancheri, Zara, and Wolf. Acquisition of data: Zara, Mathot, Nassogne, Yalcinkaya, Erturk, Tuysuz, Bugiani, Sistermans, Minetti, van der Knaap, and Wolf. Analysis and interpretation of data: Zara, Rossi, Di Rocco, Gazzerro, Bugiani, van Spaendonk, van der Knaap, and Wolf. Drafting of the manuscript: Biancheri, Zara, Nassogne, Erturk, Tuysuz, Bugiani, and Wolf. Critical revision of the manuscript for important intellectual content: Zara, Rossi, Mathot, Yalcinkaya, Di Rocco, Gazzerro, van Spaendonk, Sistermans, Minetti, van der Knaap, and Wolf. Obtained funding: Zara. Administrative, technical, and material support: Zara, Mathot, Erturk, Tuysuz, Gazzerro, Bugiani, Sistermans, and Wolf. Study supervision: Biancheri, Zara, Nassogne, Yalcinkaya, Minetti, and Wolf.

Financial Disclosure: None reported.

Funding/Support: Some samples were obtained from the Cell Line and DNA Bank From Patients Affected by Genetic Diseases collection (http://dppm.gaslini.org/biobank/), which is supported by the Italian Telethon. This study was supported in part by grant GP2007250 from the Italian Telethon, funding from the Marianni Foundation and the San Paolo Foundation, and grant 2009-03214 from the ELA Foundation.

Online-Only Material: The eTable and eFigures are available at http://www.archneurol.com.

Additional Contributions: Wouter Kamphorst, MD, assisted with the histopathologic and ultrastructural analysis.

REFERENCES


