Little folks, little myelin, and little teeth

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The leukodystrophies encompass a large and heterogeneous group of genetically determined disorders that exclusively or predominantly affect the white matter of the brain. The different disorders generally cannot be recognized on clinical grounds, since they share common, nonspecific neurologic features and lack pathognomonic signs and symptoms. MRI is pivotal in the diagnostic workup of leukodystrophies, both to demonstrate presence of a leukodystrophy and to differentiate among the many different individual disorders. The leukodystrophies can be subdivided into 2 large groups based on the presence or absence of a permanent, substantial deficit in myelin deposition in the brain, so-called hypomyelination.[1] The group of hypomyelinating leukodystrophies can further be subdivided based on additional MRI characteristics.[1,2] Although the causative genetic defect is elucidated in a rapidly growing number of these disorders, many patients remain without a definite classifying diagnosis.

In this issue of *Neurology*®, Wolf et al.[3] describe a large series of patients with so-called 4H leukodystrophy. Hypomyelination, hypodontia, and hypogonadotropic hypogonadism are the classical features of the syndrome that gave the disorder its name. In contrast to all previous reports, including recent articles on the underlying genetic cause of 4H leukodystrophy, the authors describe more than 100 patients with a DNA-proven diagnosis.[3–7] The relatively large number of well-described cases clarifies its phenotypic (including radiologic) spectrum, as well as the mutational spectrum within the 2 causative genes *POLR3A* and *POLR3B*. They show that that 4H leukodystrophy resembles the other leukodystrophies with its typical occurrence in childhood, neurologic picture dominated by mild intellectual disability, spasticity, and ataxia, slowly progressive disease course, and incomplete penetrance of associated features (here hypodontia and hypogonadism). Importantly, the large series confirms the previously described MRI characteristics,[1–3,8,9] and definitively adds 4H leukodystrophy to the recognizable hypomyelinating leukodystrophies with a known genetic cause.

Almost 10 years ago, Wolf et al.[10] described 4H leukodystrophy (not yet named as such in that publication) in 4 girls. In that report, most attention was paid to the clinical phenotype with the typical co-occurrence of hypomyelination and dental abnormalities. Other MRI abnormalities that have been identified since then, and described in the present article,[1–3,8,9] were not mentioned in that first report; however, in retrospect they can be seen in the printed figures. Although the peculiar clinical picture enabled its identification as a separate entity, the authors (and others) have meanwhile demonstrated that 3 of the 4 Hs may be absent in patients with 4H leukodystrophy, with hypomyelination as the constant finding. While this may represent a selection bias, it appears that recognition of the MRI pattern of 4H leukodystrophy enables a straightforward radiologic diagnosis that can be confirmed by direct sequencing of the *POLR3A* and *POLR3B* genes.[1–3,8,9]

Due to the rapid evolution of DNA sequencing techniques, it is expected that in the near future a growing number of patients with neurologic disorders will be diagnosed at the genetic level before the clinical or radiologic phenotype is recognized. The authors offer important data to enable the interpretation of *POLR3A* and *POLR3B* variants, once identified by genetic screening techniques like whole-exome sequencing. This article is a wonderful example of what is needed in the field of rare diseases: detailed descriptions of large series of patients, delineating the phenotypic as well as the genetic diversity of a disorder, and identifying genotype–phenotype correlations when possible.

As so often is the case in the study of rare neurologic disorders, they teach us about normal human brain development and functioning. The proteins *POLR3A* and *POLR3B* together form the active center of the 17-subunit RNA polymerase III (Pol III), which plays a central role in the (regulation of the) complex cellular machinery that translates our genetic code into proteins.[4–7] CNS myelination and teeth formation and eruption apparently are among the most vulnerable developmental processes for

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abnormal Pol III activity. One of the best known functions of Pol III is its contribution to tRNA homeostasis. Thus, 4H leukodystrophy may be added to the growing number of white matter disorders that are caused by abnormal tRNA expression.[3–7] It remains puzzling why dental abnormalities are only found in 4H leukodystrophy. It seems reasonable to hypothesize that mutations of the genes encoding for the other 15 Pol III subunits will also cause hypomyelinating leukodystrophies and dental abnormalities. The question remains whether the growing insights into the molecular basis of these neurodegenerative disorders, splitting them into individual disorders caused by defects in single genes and lumping them based on assumptions with regard to shared pathophysiologic mechanisms, will ultimately lead to the development of disease-specific, curative treatment strategies.

AUTHOR CONTRIBUTIONS

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