View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

AIMP1/p43 Mutation and PMLD

To the Editor: In the December 2010 issue of the *American Journal of Human Genetics*, Feinstein et al. reported that *AIMP1/p43* (MIM 603605) homozygous mutation causes Pelizaeus-Merzbacher-like disease (PMLD [MIM 608804]).[1] The term PMLD indicates the autosomal-recessive variant of Pelizaeus-Merzbacher disease (PMD [MIM 312080]) that is the X-linked prototype of hypomyelinating disorders. The clinical phenotype of PMLD is similar to the characteristic clinical picture of PMD and is characterized by nystagmus, impaired motor development, spasticity, and ataxia.[2,3] Seizures are exceedingly unusual. Mild peripheral neuropathy may occur in some patients.[2] The course tends to be slowly progressive. PMLD is caused by mutations in *GJC2/GJA12* (MIM 608803).[2] Brain magnetic resonance imaging (MRI) studies show diffuse cerebral hypomyelination similar to the typical MRI pattern of PMD. The presence of high T2 signal intensity of the pons has been reported as suggestive of PMLD.[4] The clinical and neuroradiological features of the patients reported by Feinstein et al.[1] seem consistent with a cortical disease rather than a primary white matter disorder. Severe failure to thrive with a concordant reduced head circumference, a rapid neurological deterioration progressing over the first months of life, and abnormal epileptiform EEG pattern suggest a cortical disease more than PMLD. On brain MRI of young children with true hypomyelination, brain atrophy is mild or absent, whereas early-onset generalized atrophy, as shown in Figures 2D–2F of the paper, points to a primary cortical degeneration. Furthermore, the reduced peak of N-acetyl aspartate found on MR spectroscopy indicates neuronal degeneration, whereas this peak is considered to be normal or high in hypomyelination.[5] In addition, the MRI criterion for a diagnosis of hypomyelination is an unchanged pattern of deficient myelination on two successive MRI scans at least 6 months apart.[6] Thus, hypomyelination cannot be diagnosed on the basis of the single MR exam of the 14-month-old girl (Figures 2D–2F of the paper), despite a similar MRI at later ages in other members of the family that might be indicative of hypomyelination.

Finally, the major role of AIMP1 in neurons[1] further supports the hypothesis that these patients may suffer from an early-onset neurodegenerative disorder causing impaired myelin formation due to neuronal dysfunction, and not from a primary defect in myelin formation/metabolism, as in PMLD.

Because hypomyelinating disorders still represent the single largest category among undiagnosed leukoencephalopathies,[4] the phenotype of possible novel genetic diseases should be correctly defined to avoid unnecessary molecular screening in PMLD patients.

As final remark, in Figure 2 of the paper,[1] panel B is not a FLAIR sequence and panel D is not a T1-weighted image (it is likely that these two images have been incorrectly labeled).

Roberta Biancheri,[1,*] Andrea Rossi,[2] Federico Zara,[3] and Mirella Filocamo[4]
[1]Child Neurology and Psychiatry Unit, Department of Neuroscience, G. Gaslini Institute, 16147 Genova, Italy; [2]Pediatric Neuroradiology, G. Gaslini Institute, 16147 Genova, Italy; [3]Muscular and Neurodegenerative Disease Unit, Department of Neuroscience, G. Gaslini Institute, 16147 Genova, Italy; [4]Laboratorio di Diagnosi pre e postnatale malattie metaboliche, G. Gaslini Institute, 16147 Genova, Italy
*Correspondence: roberta@biancheri.com

Web Resources

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/

References

1. Feinstein, M., Markus, B., Noyman, I., Shalev, H., Flusser, H., Shelef, I., Liani-Leibson, K., Shorer, Z., Cohen, I., Khateeb, S., et al. (2010). Pelizaeus-Merzbacher-like disease caused by AIMP1/p43 homozygous mutation. Am. J. Hum. Genet. *87*, 820–828.
2. Uhlenberg, B., Schuelke, M., Rüschendorf, F., Ruf, N., Kaindl, A.M., Henneke, M., Thiele, H., Stoltenburg-Didinger, G., Aksu, F., Topaloğlu, H., et al. (2004). Mutations in the gene encoding gap junction protein alpha 12 (connexin 46.6) cause Pelizaeus-Merzbacher-like disease. Am. J. Hum. Genet. *75*, 251–260.
3. Bugiani, M., Al Shahwan, S., Lamantea, E., Bizzi, A., Bakhsh, E., Moroni, I., Balestrini, M.R., Uziel, G., and Zeviani, M. (2006). GJA12 mutations in children with recessive hypomyelinating leukoencephalopathy. Neurology *67*, 273–279.
4. Steenweg, M.E., Vanderver, A., Blaser, S., Bizzi, A., de Koning, T.J., Mancini, G.M., van Wieringen, W.N., Barkhof, F., Wolf, N.I., and van der Knaap, M.S. (2010). Magnetic resonance imaging pattern recognition in hypomyelinating disorders. Brain *133*, 2971–2982.
5. Hanefeld, F.A., Brockmann, K., Pouwels, P.J., Wilken, B., Frahm, J., and Dechent, P. (2005). Quantitative proton MRS of Pelizaeus-Merzbacher disease: Evidence of dys- and hypomyelination. Neurology *65*, 701–706.
6. Schiffmann, R., and van der Knaap, M.S. (2009). Invited article: An MRI-based approach to the diagnosis of white matter disorders. Neurology *72*, 750–759.

DOI 10.1016/j.ajhg.2011.02.003. ©2011 by The American Society of Human Genetics. All rights reserved.