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Brain Magnetic Resonance Imaging (MRI) Pattern Recognition in Pol III-Related Leukodystrophies

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Abstract

Pol III-related leukodystrophies are caused by mutations in *POLR3A* and *POLR3B* genes and all share peculiar imaging and clinical features. The objectives of this study are (1) to define the neuroradiologic pattern in a cohort of *POLR3A* and *POLR3B* subjects and (2) to compare the neuroradiologic pattern of Pol III-related leukodystrophies with other hypomyelinating disorders. The magnetic resonance imaging (MRI) examinations of 13 patients with *POLR3A* and *POLR3B* mutations and of 14 patients with other hypomyelinating disorders were analyzed. All the subjects with Pol III-related leukodystrophies presented hypomyelination associated with T2 hypointensity of the thalami and/or the pallida. Twelve subjects (92%) presented T2 hypointensity of the optic radiations. Cerebellar atrophy was observed in most patients (92%). The combination of the analyzed criteria identified patients with Pol III-related leukodystrophies with a sensitivity of 84.6% and a specificity of 92.9%.

Keywords

leukodystrophy, magnetic resonance imaging, hypomyelination

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Hypomyelinating leukodystrophies represent the majority of leukoencephalopathies of undetermined origin in infancy.[1] Magnetic resonance imaging (MRI) pattern recognition is now an essential tool in categorizing them and has enabled the definition of new entities, in particular among hypomyelinating disorders.[2,3] Pol III-related leukodystrophies constitute a recently genetically defined group of hypomyelinating leukodystrophies that include different previously described conditions with often specific MRI white matter involvement.[4-6] Leukodystrophy with oligodontia was the first entity of this group of diseases to be described in 2003 in a Syrian family.[7] In 2005, Wolf et al[4] described 4 patients with a similar disorder characterized by hypomyelination, ataxia, and abnormal dentition.[4,5] Following these descriptions, a growing number of patients with hypogonadotropic hypogonadism in association with hypomyelination and abnormal dentition were identified by different groups and referred to as 4H syndrome.[8,9-11] The original family with leukodystrophy and oligodontia and Quebec families with an overlapping phenotype were found to be allelic, with mapping to 10q22 region[12] for leukodystrophy with oligodontia and 10q22.3–10q23.31 for tremor ataxia with central hypomyelination.[13] In 2011, mutations in 2 genes (*POLR3A*[14,15] and *POLR3B*[15,16]) encoding the 2 largest subunits of RNA polymerase III (Pol III) were identified in subjects with leukodystrophy with oligodontia, 4H, and tremor ataxia with central hypomyelination. At this time, a total of 5 different overlapping conditions, including 4H syndrome, leukodystrophy with oligodontia,[7] ataxia delayed dentition and hypomyelination,[4,5] tremor-ataxia with central hypomyelination,[13] and hypomyelination with cerebellar

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Table 1. Logistic Regression Results: Model Developed Using Team Gold Standard Assessments.

Criterion	OR	*P* value	95% CI
Hypo T2 thalamus	10.56	.144	0.44-249.86
Hypo T2 pallida	18.08	.090	0.64-511.35
Hypo T2 pyramidal tracts and/or posterior periventricular WM	11.04	.420	0.03-3801.72
Hypo T2 dentate	17.02	.095	0.61-473.78
Cerebellar atrophy	37.28	.106	0.47-2984.65

Abbreviations: CI, confidence interval; Hypo T2, hypointense signal in T2-weighted images; OR, odds ratio; WM, white matter.

atrophy and hypoplasia of the corpus callosum,[15,17] have been found to be caused by recessive mutations in *POLR3A*[13-15] or *POLR3B*.[15,16] These disorders likely represent a continuum of clinical manifestations. No detailed phenotype-genotype correlation has been completed to date. These disorders are now globally referred to as Pol III-related leukodystrophies.

The 2010 manuscript by Steenweg et al[3] described a distinctive neuroradiologic pattern in subjects with 4H syndrome prior to the identification of mutation. This pattern includes: supratentorial diffuse hypomyelination variably associated with T2 hypointensity of the optic radiations, the pyramidal tracts at the level of the posterior limb of the internal capsule, the anterolateral nuclei of the thalami and the pallida. The presence of cerebellar atrophy, mostly vermian, and a relative T2 hypointensity of the dentate nuclei compared to the surrounding cerebellar white matter completes the picture.

Our study aims at further describing the neuroradiologic findings of Pol III-related hypomyelinating leukodystrophies as well as validating the above MRI characteristics in a sample of mutation-proven patients.

Methods

Participants and Data Collection

Brain MR images of 13 patients (5 females, 8 males; mean age at MRI = 17.8 years, range = 4-32 years) with a clinical diagnosis of 4H or tremor ataxia with central hypomyelination were collected. The diagnosis of Pol III-related leukodystrophy was confirmed by Sanger sequencing in all patients, revealing pathogenic recessive mutations in either the *POLR3A* (10 subjects) or *POLR3B* (3 subjects).

Fourteen control subjects (2 females, 12 males; mean age at MRI = 6.2 years, range = 4 months-32 years) with other identified hypomyelinating disorders were selected among our database. The clinical features and the age at MRI of Pol III subjects and controls are summarized in Supplemental Table 1 (Supplemental Table 1 is available at http://jcn.sagepub.com/Supplemental). Given the rarity of these diseases, matching controls for age and sex were sought, but the mean age of the Pol III mutation–positive subjects was greater, partly because of the relatively milder phenotype of Pol III-related leukodystrophies compared with the other hypomyelinating leukodystrophies and partly because of the greater likelihood that they were identified after the expected age of puberty. For both reasons, Pol III mutation subjects are more likely to have MRIs at an older age. Because of the potential biases that could arise from the age difference between the 2 groups, the presence of the analyzed criteria was evaluated in relation to the age of the subject.[18] The control group included 6 subjects with Pelizaeus-Merzbacher disease, 2 with Pelizaeus-Merzbacher–like disease caused by *GJC2* mutations, 2 with Salla disease, 2 with hypomyelination with atrophy of the basal ganglia and cerebellum, and 2 with infantile GM1 gangliosidosis. Except for hypomyelination with atrophy of the basal ganglia and cerebellum, these were the same disorders studied in the original algorithm for hypomyelinating leukodystrophies by Steenweg et al.[3]

As the MR images were performed in different centers and sent to our team for diagnostic purpose, variability in the technique and acquisition of images was observed. However, sagittal T1-weighted images and axial T2- and axial FLAIR-weighted images were available for all the subjects, allowing the evaluation of the selected criteria. For 10 patients, axial T1 and/or sagittal T2 were also available.

Data Analysis

The neuroradiologic findings were analyzed according to the following criteria: presence of diffuse hypomyelination, cerebellar atrophy, and T2 hypointensity of the anterolateral thalami, pallida nuclei, pyramidal tracts, posterior periventricular white matter (in the region of the optic radiations) and dentate nuclei.

All images were reviewed by our team collegially (A.V., G.B., D.T. and R.L.). Team disagreements were resolved by consensus. In addition, images were reviewed on 2 different occasions by an experienced neuroradiologist (J.M.), without specific experience in leukodystrophies who was blind to the clinical and molecular data. The 2 reviews of the images were separated in time by 6 weeks, in order to avoid memory of individual subjects.

Statistical Analysis

Logistic regression analysis was used to describe how the proposed criteria by Steenweg et al (2010)[3] compare in Pol III-related leukodystrophies versus other hypomyelinating leukodystrophies. A model including all examined criteria was initially used to evaluate the association between all the criteria and the diagnosis of Pol III-related leukodystrophies as well as the sensitivity and specificity of these criteria. The fit of the model was tested using the Homer-Lemeshow goodness-of-fit test. Moreover, criteria were analyzed individually and in pairs of similar findings: T2 hypointensity of the pyramidal tracts and optic radiations individually and together; T2 hypointensity of the pallida nuclei and anterolateral nuclei of the thalami individually and together; cerebellar atrophy; and T2 hypointensity of the dentate nuclei. These analyses were performed using the team evaluation data. All statistical analyses were performed using Stata V11 (College Station, TX).

Interoperator agreement (namely, agreement between team and radiologist's reading 1 and reading 2) and intraoperator agreement (namely, the agreement between radiologist's reading 1 and 2) were evaluated using Kappa statistics. According to Landis,[19] we considered Kappa statistics $\geq$0.81 as almost perfect agreement, 0.61 to 0.80 as substantial, 0.41 to 0.60 as moderate, 0.21 to 0.40 as fair, and 0 to 0.20 as slight agreement.

Results

The data presented below correspond to the review by the evaluating team as a group, unless otherwise specified (see Interoperator and Intraoperator Agreement section).

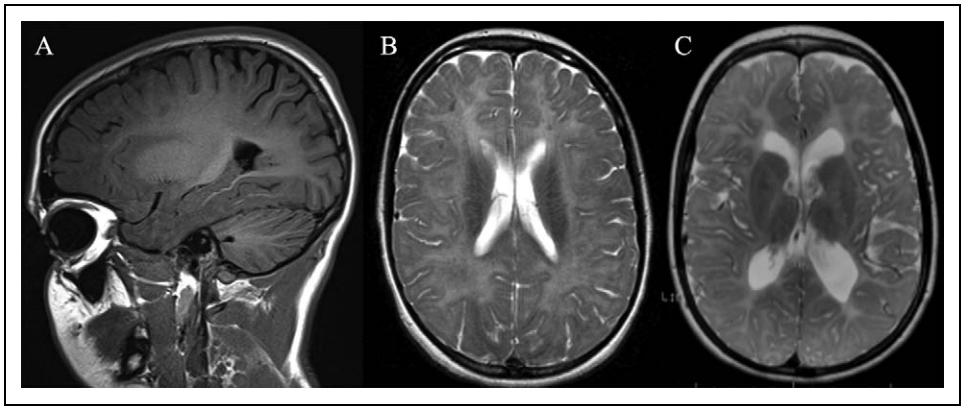

Figure 1. Hypomyelination in Pol III-related leukodystrophies. Sagittal T1-weighted (A) and axial T2-weighted images (B, C) demonstrate the presence of diffuse and homogeneous hypomyelination in 2 patients: 17-year-old male subject with *POLR3B* mutation shown in A, B; 10-year-old male subject with *POLR3A* mutation shown in C. Hypomyelination is defined here as isointense or hyperintense T1 signal and hyperintense T2 signal.

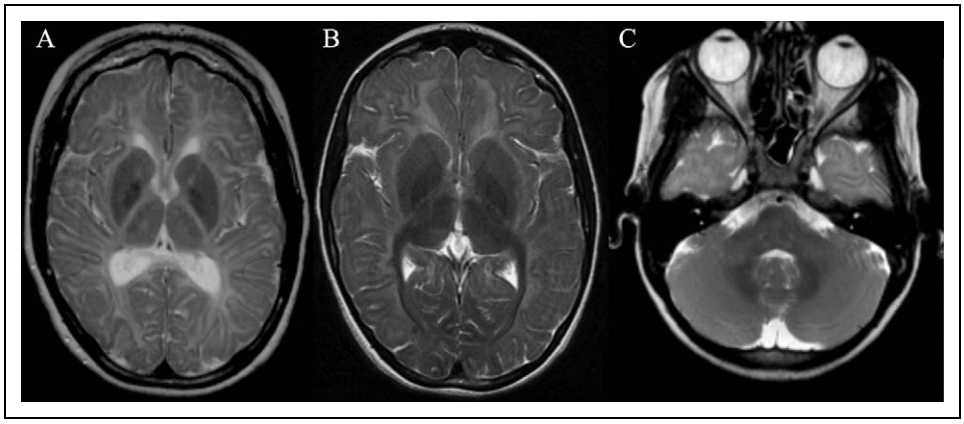

Figure 2. Features associated with diffuse hypomyelination in Pol III-related leukodystrophies. Twenty-two-year-old male subject with *POLR3A* mutation in A; 17-year-old male subject with *POLR3B* mutation in B; 11-year-old male subject with *POL3A* mutation in C. Axial T2-weighted images showing the presence of hypointense signal at the level of the anterolateral nuclei of the thalami and of the pallida bilaterally (A, B), of the optic radiations (A, B) and corticospinal tracts (B), and of the dentate nuclei (C).

Neuroradiologic Findings in Pol III-Related Leukodystrophies

The presence of diffuse hypomyelination was observed in all 13 mutation-proven Pol III-related leukodystrophy patients (100%) (Figure 1). It was associated with T2-weighted hypointensity in the regions of the pallida and/or thalami in all subjects (13/13; 100%) (Figure 2A, B). In 10 patients (10/13; 77%), the low T2 signal was seen both in the anterolateral portion of the thalami and in the pallida nuclei, whereas in 2 patients (2/13; 15%) it was limited to the anterolateral portion of the thalami and in 1 (1/13; 8%) to the pallida nuclei.

A relative low T2 signal of the dentate nuclei in comparison to the surrounding white matter was observed in 9 patients (9/13; 69%) (Figure 2C). Twelve subjects (12/13; 92%) presented T2 hypointense signal in the posterior periventricular white matter; the optic radiations were hypointense in T2-weighted images in all 12 patients while in 1 subject the T2 hypointensity extended to the adjacent tapetum (Figure 2B). The pyramidal tracts at the level of the posterior limb of the internal capsule presented a T2 hypointense signal in 5 subjects (5/13; 38%). Cerebellar atrophy was observed in 12 patients (12/13; 92%), involving both the cerebellar hemispheres and the vermis (Figure 3). Three patients (23%) presented all MRI features analyzed.

Neuroradiological Findings in Other Hypomyelinating Leukodystrophies (Non Pol III-Related)

As for subjects with non–Pol III-related leukodystrophies, diffuse hypomyelination was observed in the totality of the group (14/14; 100%). T2 hypointensity in the region of the pallida and/or thalami was found in 4 subjects (4/14; 29%). In 2 patients (2/14; 14%), the low T2 signal involved both the thalami and the pallida, whereas in 1 patient (1/14; 7%) it was limited to the thalami and in another 1 (1/14; 7%) to the pallida. T2 hypointense signal was also observed in the pyramidal tracts at

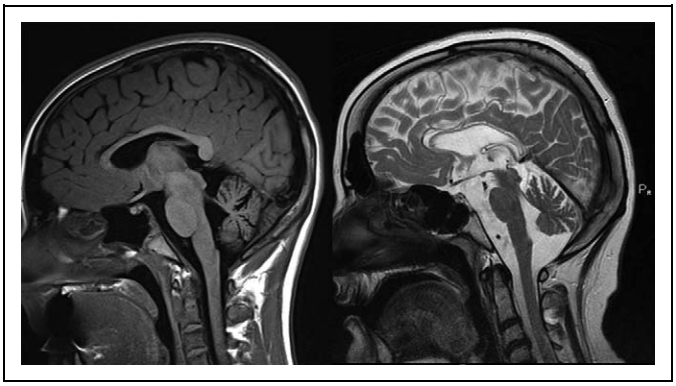

Figure 3. Cerebellar atrophy in Pol III-related leukodystrophy. Midline sagittal T1-weighted (left) and T2-weighted (right) images in 2 patients showing variable degrees of vermian atrophy (left, 17-year-old male subject with *POLR3B* mutation; right, 8-year-old male subject with *POLR3A* mutation).

the level of the posterior limb of the internal capsule in 9 patients (9/14; 64%), in the dentate nuclei in 3 (3/14; 21%), and in the posterior periventricular white matter in 6 patients (6/14; 43%). Cerebellar atrophy was present in 8 subjects (8/14; 57%), including as expected the 2 subjects with hypomyelination with atrophy of the basal ganglia and cerebellum.

No subject from our control group presented all typical MRI features for Pol III-related leukodystrophies.

MRI Pattern Recognition

The direct comparison of MRI findings between patients with Pol III-related hypomyelinating leukodystrophies and the control group formed by other hypomyelinating disorders is illustrated in Figure 4. All the features, with the exception of cerebellar atrophy and pyramidal tract hypointense signal, were statistically significantly more likely to be seen in the Pol III-related patients than in controls, with T2-weighted hypointensity in the regions of the pallida ($P = .003$) and thalami ($P = .002$) showing the highest significance. Pyramidal tract T2-hypointensity was more often seen in controls than in Pol III patients, though without reaching statistical significance.

The combination of all criteria—(1) T2 hypointensity of the globi pallidi, (2) T2 hypointensity of the anterolateral thalami, (3) T2 hypointensity of the pyramidal tracts and/or the periventricular white matter, (4) T2 hypointensity of the dentate nuclei, and (5) cerebellar atrophy—was associated by the logistic regression model to Pol III-related leukodystrophy in 88.9% of patients with a sensitivity of 84.6% and specificity of 92.9% (goodness of fit $P = .77$) (Table 1).

The presence of each criterion, in conjunction with all the others, was more likely to be found in Pol-III related leukodystrophy (odds ratios reported in Table 1). However, for all the criteria, the 95% of confidence interval was very wide and no statistical significance was reached for any individual criteria.

When logistic regression included the presence of either T2 hypointensity of the anterolateral thalami and/or pallida nuclei, all Pol III patients were correctly classified. If there was T2 hypointensity of neither the lateral thalamus nor globus pallidus, patients could therefore be reliably categorized as unlikely to have Pol III-related leukodystrophies (Table 2; $P < .001$).

Interoperator and Intraoperator Agreements

We analyzed the agreement between the expert team review and the 2 neuroradiologists' reviews blind to clinical data. The agreement between the 2 radiologist reviews (intraobserver agreement) and between each of the radiologist reviews and the team consensus (interobserver agreement) resulted in concordance in the majority of cases (Supplementary Tables 2 and 3 [Supplemental Tables 2 and 3 are available at http://jcn.sagepub.com/Supplemental]). The agreement was particularly high for the findings of T2 hypointensity of pyramidal tracts and dentate and for cerebellar atrophy. For intraobserver agreement (Table 1), the 2 different evaluations performed by the same neuroradiologist, T2 hypointensity of pyramidal tracts (κ value $= 0.85$), T2 hypointensity of dentate nuclei (κ value $= 0.84$), and cerebellar atrophy (κ value $= 0.92$) resulted in perfect agreement.

Similarly, for interobserver agreement (Supplementary Table 3) each of the evaluations from the blinded neuroradiologist was compared to the consensus of the team. Although without reaching values of perfect agreement, kappa statistics were high for the same features: T2 hypointensity of pyramidal tracts (κ statistic $= 0.62$ and 0.77), T2 hypointensity of dentate nuclei (κ statistic $= 0.70$ and 0.70), and cerebellar atrophy (κ statistic $= 0.60$ and 0.54).

Discussion

This is the first systematic analysis of the neuroradiologic findings in a cohort of *POLR3A* and *POLR3B* mutation-proven patients. There is only 1 other recent qualitative study looking at the presence of cerebellar atrophy and hypomyelination in a cohort of 6 Japanese patients with Pol III-related leukodystrophies.[20] Our study supports the reliability of all the MRI features proposed by Steenweg et al[3] applicable for Pol III-related leukodystrophies.[3]

The association of all the criteria (ie, T2 hypointensity of the pallida, anterolateral nuclei of the thalami, dentate nuclei and pyramidal tracts, or periventricular white matter and cerebellar atrophy) was present in the large majority of Pol III-related leukodystrophies in this small sample set. No patients with non–Pol III-related leukodystrophy met all of these criteria. In particular, the presence of T2 hypointensity at the level of the anterolateral portion of the thalami and/or the pallida was found to be highly useful to identify patients with Pol III-related leukodystrophies. In other words, in this cohort of mutations-proven subjects with Pol III-related compared to a cohort of other hypomyelinating leukodystrophies, the absence of T2 hypointensity of the pallida and of the anterolateral thalami makes the diagnosis of Pol III-related leukodystrophy less likely. Although in this data set no patient with Pol III related

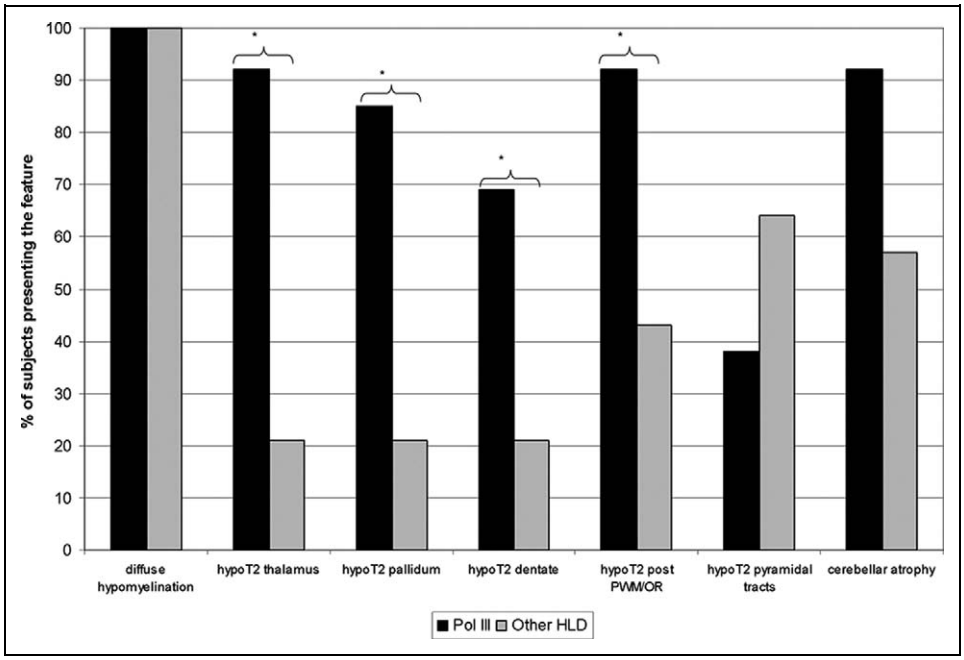

Figure 4. Graphic representation of the different MRI features for the group of Pol III-related leukodystrophies versus the group of hypomyelinating leukodystrophies of other etiologies. The asterisk (*) indicates a statically significant difference ($P < .05$, Fisher exact test) in the presence of the feature between Pol III-related leukodystrophy patients and controls. Abbreviations: HLD, hypomyelinating leukodystrophies; hypoT2, hypointensity of the white matter on T2-weigthed MRI; Pol III, Pol III-related leukodystrophies; PWM, periventricular white matter; OR, optic radiations.

Table 2. Presence of T2 Hypointensity of the Anterolateral Nuclei of the Thalami and/or Globi Pallidi in Pol III-Subjects Versus Controls According to the Team's Review.

Status	No	Yes	Total
Control subject	10	4	14
Pol III subject	0	13	13
Total	10	17	27

leukodystrophy had either T2 hypointensity of the thalami or of the globus pallidus, we cannot exclude, in view of the relatively small sample size, that this would be the case in all Pol III-related leukodystrophy patients. We suggest however, that in the presence of diffuse hypomyelination and T2 hypointensity of the anterolateral nuclei of the thalami and/or the globi pallidi, the sequencing of the *POLR3A* and *POLR3B* genes should be requested. As expected based on the existing literature,[5,10,13] cerebellar atrophy was found in 92% of patients with Pol III-related leukodystrophy. Consequently, the absence of cerebellar atrophy does not rule out the diagnosis of Pol III-related leukodystrophy. The same feature was seen only in half of the subjects with other hypomyelinating leukodystrophies, among which were 2 subjects with hypomyelination with atrophy of the basal ganglia and cerebellum syndrome. Consequently, we suggest that in the presence of cerebellar atrophy and diffuse hypomyelination, the sequencing of the *POLR3A* and *POLR3B* genes should be considered, especially if there is no atrophy of the putamen.

The neuroradiologic pattern of Pol III-related leukodystrophies is quite characteristic. However, other hereditary diseases can be included in the differential diagnosis of Pol III-related leukodystrophies based on the co-occurrence of specific features. Among hypomyelinating disorders, cerebellar atrophy can be found in hypomyelination with atrophy of the basal ganglia and cerebellum, Salla disease,[3,21,22] and Cockayne syndrome.[21,23] Hypomyelination can be found in association with T2 hypointensity of the globi pallidi in fucosidosis[24] and of the thalami in oculodentodigital dysplasia.[25]

The first limitation of this study, as is often the case in studies on rare diseases, was that the sample size was relatively small. We have used this small sample set of 27 subjects to evaluate 5 criteria as suggestive of the diagnosis, possibly leading to overfitting of the model. Moreover, the mean age of 2 groups (Pol III vs controls) was markedly different because of the rarity of these disorders and to the milder phenotype of Pol III-related leukodystrophies. This could lead to biases in the evaluation of some MRI criteria that vary with age (ie, T2 hypointensity of the globi pallidi). To limit this potential bias, we evaluated the presence of each criterion in relation to the age of the patient. The second limitation was that the core team of investigators was not blind to the genetic diagnosis. This was due to the fact that the study was retrospectively done and the selected patients were positive for mutation analysis of *POLR3A* and *POLR3B* genes. We are aware that this bias could lead to an overestimation of positive findings in the case group.[26] For this reason, an experienced neuroradiologist reviewed and interpreted the images without knowledge of the

final diagnosis. The neuroradiologist's evaluation demonstrated good consistency with the team's review. It should be noted that although T2 hypointensity of the thalamus and globus pallidus were the best indicators of Pol III-related leukodystrophy, their intra- and interobserver agreement where slightly less significant than that of the other criteria. The high concordance between the 2 reviews performed by the same neuroradiologist can be a measure of the reproducibility of our results; moreover, it suggests that the proposed criteria, when present, are evident. It is reassuring to note that the characteristic features were reliably identified by a blinded pediatric neuroradiologist with no prior experience with Pol III-related disorders. Thus, these proposed MRI criteria are likely to be useful in a clinical setting, in particular for the identification of less constant features such as the T2 hypointensity of pyramidal tracts, T2 hypointensity of dentate nuclei, and cerebellar atrophy. Finally, we are aware that our sample size is not adequate to develop and test a prediction model; nonetheless, our model shows that each of these variables might be informative for diagnosis.

In conclusion, our study confirmed that the MRI pattern recognition of patients with mutation-proven Pol III-related leukodystrophies is characterized by diffuse hypomyelination associated with cerebellar atrophy and T2 hypointensity in the pallida, anterolateral nuclei of the thalami, dentate, optic radiations, and pyramidal tracts. These criteria can be helpful in the clinical setting to distinguish Pol III-related leukodystrophies among hypomyelinating disorders and, thus, to orient the clinical and molecular diagnostic workup.

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Author Contributions

RLP and DT are first authors who contributed equally to this work. AV and GB are mentors who contributed equally to this work. GB and AV conceived and designed the study and, along with BB, critically revised the manuscript for important intellectual content. RLP and DT drafted the paper. JLS and AV acquired the data. RLP, DT, GB, and AV were responsible for analysis and interpretation of data. HGD performed the statistical analysis and JM analyzed the neuroradiologic data HDG and JM critically revised the manuscript.

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 study received internal ethical approval from the Children's National Medical Center Institutional Review Board (Ethic approval number Pro00000057) and from the Montreal Children's Hospital Research Ethics Board (Ethic approval number 11-105-PED).

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