REPORT

Adult-onset genetic leukoencephalopathies: A MRI pattern-based approach in a comprehensive study of 154 patients


*These authors contributed equally to this work.

Inherited white matter diseases are rare and heterogeneous disorders usually encountered in infancy. Adult-onset forms are increasingly recognized. Our objectives were to determine relative frequencies of genetic leukoencephalopathies in a cohort of adult-onset patients and to evaluate the effectiveness of a systematic diagnostic approach. Inclusion criteria of this retrospective study were: (i) symmetrical involvement of white matter on the first available brain MRI; (ii) age of onset above 16 years. Patients with acquired diseases were excluded. Magnetic resonance imaging analysis identified three groups (vascular, cavitary and non-vascular/non-cavitary) in which distinct genetic and/or biochemical testing were realized. One hundred and fifty-four patients (male/female = 60/94) with adult-onset leukoencephalopathies were identified. Mean age of onset was 38.6 years. In the vascular group, 41/55 patients (75%) finally had a diagnosis [including CADASIL (cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy, n = 32) and COL4A1 mutation, n = 7]. In the cavitary group, 13/17 (76%) patients had a diagnosis of EIF2B-related disorder. In the third group (n = 82), a systematic biological screening allowed a diagnosis in 23 patients (28%) and oriented direct genetic screening identified 21 additional diseases (25.6%). Adult-onset genetic leukoencephalopathies are a rare but probably underestimated entity. Our study confirms the use of a magnetic resonance imaging-based classification with a final diagnosis rate of 64% (98/154) cases.

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Introduction

Inherited white matter diseases are heterogeneous neurodegenerative diseases. They include hypomyelinating (abnormal myelin development) and demyelinating (myelin degeneration) leukodystrophies.

In a recent paediatric study, their overall estimated incidence was 1/7603 live births, with a definitive diagnosis in half of them (Bonkowsky et al., 2010). Main causes were metachromatic leukodystrophy (8.2%), Pelizaeus-Merzbacher disease (7.4%), mitochondrial diseases (4.9%), and X-linked adrenoleukodystrophy (4.1%).

Adult-onset inherited white matter diseases are considered as rare. Therefore, a comprehensive study has not been previously published. The objectives of our study were to identify patients with adult-onset inherited white matter diseases in a large nationwide study and to evaluate the interest of a systematic diagnostic approach based on MRI pattern (Labauge et al., 2014).

Materials and methods

Patients

This multicentric retrospective study included all the multiple sclerosis centres in France between January 2007 and
July 2012. All the medical records of patients referred for a possible genetic leukoencephalopathy were reviewed. Inclusion criteria were: (i) symmetrical and confluent white matter hyperintensities on T2-weighted MRI; and (ii) clinical age of onset above 16 years. Patients with evidence of an acquired disease were excluded. Required MRI investigation included T1, T2, FLAIR and gradient echo sequences.

Clinical data were reviewed by three neurologists (C.C.D., X.A., P.L.) and MRI analysed by a neuroradiologist (N.M.) and three neurologists (C.C.D., X.A., O.B.T.). According to MRI findings, patients were classified in three groups:

Group 1: Vascular leukoencephalopathy based on occurrence of hyperintensities involving the deep grey matter, the pons and the external capsules, lacunes on T2/FLAIR sequences. Presence of microbleeds on gradient echo sequence confirmed the vascular disease (Pantoni et al., 2010).

Group 2: Cavitary leukoencephalopathy, defined by extensive hypointensities within large areas of hyperintensities on FLAIR sequences (van der Knaap et al., 2006; Labauge et al., 2009).

Group 3: This heterogeneous group included patients with white matter hyperintensities, without any argument for a vascular mechanism or a cavitary leukoencephalopathy.

**Molecular and biochemical screening**

In Group 1, the NOTCH3 gene [involved in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)] was systematically sequenced. Patients with MRI and/or clinical phenotype suggestive of COL4A1-related disorders (Vahedi and Alamowitch, 2011) underwent sequencing of the entire COL4A1 gene (Vahedi et al., 2003). Occurrence of progressive cysts, calcifications and gadolinium enhancement on MRI (Kleinschmidt-Demasters et al., 2009) led to a diagnosis of leukoencephalopathy with calcifications and cysts, without any known mutated gene.

In Group 2, screening of the EIF2B1–5 genes causing the childhood ataxia with CNS hypomyelination disease was systematic (Fogli et al., 2004).

In Group 3, investigations were conducted in two steps. First, an inborn error of metabolism was searched in all of the cases. The systematic screening included the research of lysosomal disorders (beta-hexosaminidase, beta-galactosidase, beta-glucocerebrosidase, beta-galactocerebroside, alpha-galactosidase, arylsulfatase A, alpha-l-fucosidase, alpha-mannosidase, beta-mannosidase, arylsulfatase B, beta-glucuronidase), research of peroxysomal disorders (very long chain fatty acid levels), cholestanol levels, homocysteine and glucuronidase), research of peroxysomal disorders (beta-hexosaminidase, beta-galactosidase, beta-glucocerebrosidase, beta-galactocerebroside, alpha-galactosidase, arylsulfatase A, alpha-l-fucosidase, alpha-mannosidase, beta-mannosidase, arylsulfatase B, beta-glucuronidase), research of peroxysomal disorders (very long chain fatty acid levels), cholestanol levels, homocysteine and urinary glycosphingolipids. Enzymatic deficiency was confirmed by genetic analysis.

In patients without any detected enzyme deficiency, clinical and MRI findings were carefully reviewed. Clinical analysis focused on transmission (recessive, dominant, X-linked), neurological and extraneurological findings (e.g. syndactyly). MRI pattern analysis focused on specific features (Ahmed et al., 2014) to directly sequence pathogenic genes involved in specific disease.

**Standard protocol approvals, registrations and patient consents**

Written informed consent was obtained from patients (or their guardians) participating in the study. Protocol approvals was obtained from ethical committee of the ‘centre de protection des personnes Sud-Est VI’, France

**Results**

Among 311 submitted files, 154 (male/female = 60/94) fulfilled the inclusion criteria (Fig. 1). Clinical findings were: age of onset of 38.6 years (range 16–75); initial symptoms: spastic paraparesis (n = 47), cerebellar ataxia (n = 33), cognitive decline (n = 29), psychiatric symptoms (n = 22: psychotic n = 9; depressive, n = 13) and stroke (n = 23). Based on MRI findings, patients were classified as follows: Group 1 (55/154), Group 2 (17/154), Group 3 (82/154) (Fig. 1). Familial history was noted in 43 patients (27.7%), suggestive of a dominant pattern of inheritance in 22. The exact transmission was unavailable in 21 cases.

**Group 1: Vascular disease**

This group includes 55 patients [male/female: 22/33; mean age at onset: 41.5 (range: 17–72)]. Forty-one patients (75%) had a diagnosis: 32 CADASIL, seven COL4A1-related disorder and two leukoencephalopathy with calcifications and cysts. Fourteen patients remained without diagnosis.

Of the 32 (58%) patients (male/female: 15/17) with a pathogenic NOTCH3 gene mutation (Fig. 2A), a positive familial history was found in 11/32, suggestive of dominant inheritance in 10. Clinical findings were: mean age of onset: 38.6 years (range: 18–59); initial symptoms: stroke (n = 13), cognitive impairment (n = 3) and depression (n = 5). In 12 patients, MRI was done for non-specific symptoms (including migraine with or without aura in eight). Most of the patients had a brain MRI suggestive of CADASIL with frequent involvement of brainstem, external capsules and temporal lobe (Fig. 2A).

COL4A1 gene mutations were found in seven cases (male/female: 4/3). Clinical findings were: mean age of onset: 37.4 (range: 17–72); initial symptoms: intracerebral haemorrhage (n = 2), ischaemic stroke (n = 1), cognitive impairment (n = 1) and fortuitous diagnosis in three. Only two patients had extraneurological features (cataract, retinal arteriolar tortuositities) suggestive of COL4A1 mutation. MRI patterns consisted of: vascular leukoencephalopathy (100%), porencephalic cavities (28%) (Fig. 2B), deep calcifications (83%) and microbleeds (85%). All had internal capsules involvement without any temporal involvement. Dominant inheritance was found in 2/7 cases.

Two patients (male/female: 1/1) had a leukoencephalopathy with calcifications and cysts diagnosis based on the presence of extensive cysts, with calcifications and...
Figure 1  Study design and classification of the adult-onset leukoencephalopathies. CACH/VWM = childhood ataxia with central nervous system hypomyelination syndrome/vanishing white matter disease; LCC = leukoencephalopathy with calcifications and cysts; WM = white matter.

Figure 2  Cerebral MRI illustrating the main results. (A–B) Axial FLAIR images; (C) enhanced T1-weighted sequence; (D) CADASIL; (E) COL4A1 mutation; (F) leukoencephalopathy with calcifications and cysts; (G) vascular leukoencephalopathy without diagnosis; (H) childhood ataxia with central nervous system hypomyelination syndrome/vanishing white matter disease; (I) X-linked adrenoleukodystrophy; (J) cerebro-tendinous xanthomatosis; and (K) Krabbe disease.
gadolinium enhancement in all the patients (Fig. 2C). Mean age of onset was 30.5 years (range 30–31). Initial symptoms were stroke in one patient and non-specific in one.

Finally, 14 patients with a vascular leukoencephalopathy remained without diagnosis. Clinical and MRI findings in these 14 patients (Fig. 2D) and in those with NOTCH3 gene pathogenic mutations (n = 32) were not different, except of a more frequent temporal involvement in the CADASIL group (87% versus 62%). Interestingly, a positive familial history, suggestive of an autosomal dominant inheritance, was found in 2 of these 14 patients.

**Group 2: Cavitary disorder**

Thirteen patients (76%) had a pathogenic EIF2B mutation, establishing the diagnosis of adult-onset EIF2B-related disorders (childhood ataxia with central nervous system hypomyelination syndrome). Clinical findings were: sex ratio imbalance (male/female: 3/14), age of onset: 39 years (range 16–57), initial symptoms: cognitive impairment (n = 8), pyramidal symptoms (n = 7), psychiatric disorder (n = 5), including depression in three and psychotic disorder in two and cerebellar ataxia (n = 5). MRI consisted of extensive white matter T2/FLAIR hyperintensities with hypointensities on T1/FLAIR sequences (Fig. 2E). MRI features were similar in mutated and non-mutated patients. Seven patients had the homozygous mutation c.338G>A mutation (p.R113H) in the EIF2B5 gene.

**Group 3: Magnetic resonance without vascular or cavitary aspects**

This group includes 82 patients (male/female: 34/48) with a mean age of onset of 35.9 years (range: 16–75). Initial symptoms were spastic paraparesis (n = 35), cerebellar ataxia (n = 25), cognitive decline (n = 16), psychiatric symptoms (n = 11: five depression / six psychotic), movement disorder (n = 5), seizures (n = 2) and non-specific in six.

Our extensive metabolic investigation led to identify the aetiologic diagnosis in 23 cases including X-linked adrenoleukodystrophy (n = 11; Fig. 2F), cerebrotendinous xanthomatosis (n = 5; Fig. 2G), Krabbe disease (n = 3; Fig. 2H), metachromatic leukodystrophy (n = 2), α-mannosidosis (n = 1) and methionine synthetase deficiency (n = 1).

A detailed analysis of MRI and clinical features allowed us to identify a definitive diagnosis in 21 patients (Table 1): fragile X-associated tremor ataxia syndrome (n = 4; Fig. 3A), hereditary spastic paraplegia (SPG10, n = 1, SPG11: n = 2; Fig. 3B), oculodentodigital syndrome (n = 2; Fig. 3C), leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate (n = 2; Fig. 3D), autosomal dominant leukodystrophy (n = 2; Fig. 3E), mitochondrial disease (n = 3; Fig. 3F), hereditary diffuse leukoencephalopathy with spheroids (n = 2; Fig. 3G), X-linked Charcot–Marie–Tooth disease (n = 1; Fig. 3H), Pelizaeus-Merzbacher disease (n = 1) and adult onset polyglucosan body disease (n = 1). Finally, 38 patients of this group remained without diagnosis.

**Discussion**

This series is the first focusing on adult-onset genetic leukoencephalopathies. The high rate of confirmed diagnosis (64%) in the whole cohort (98/154), reaching 75% and 76% in the vascular and cavitary groups, respectively confirms the usefulness of our MRI classification, based on three MRI pattern groups with separate diagnostic work-up.

Indeed, adult-onset leukoencephalopathy aetiologies are quite various, with time-consuming and expensive investigations (Ahmed et al., 2014). MRI-based diagnostic algorithms have been mainly proposed in children with genetic leukodystrophies (Schiffrin and van der Knaap, 2009). The major discriminant was the presence of hypomyelinating leukoencephalopathy, which is rarely encountered in adult-onset leukoencephalopathies (Steenweg et al., 2010). On the contrary, large series of patients with vascular (CADASIL, COL4A1-related disorders, etc) or cavitary disorders (childhood ataxia with central nervous system hypomyelination/vanishing white matter disease) have been described (Dichgans et al., 1998; Labauge et al., 2009). Therefore, we focused on the presence of vascular or cavitary findings to simplify the further diagnostic work-up in each group.

Family history is usually considered as a major discriminant in the diagnostic work-up of inherited disorders. Familial occurrence was observed in only 42 probands, suggesting autosomal dominant inheritance in 22. Most (n = 15/22) were in the vascular group. The final seven cases were from the third group, with a definitive diagnosis in three: autosomal dominant leukodystrophy, hereditary diffuse leukoencephalopathy with spheroids and oculodentodigital syndrome. No specific mode of inheritance could be defined in 16 patients. The relative low rate (28%) of positive familial history can be explained by recessive inheritance, incomplete penetrance, censoring effect or de novo mutation. At least, acquired diseases cannot be formally excluded.

The first group included vascular diseases, based on involvement of the grey matter, lacunar infarcts and microbleeds. Such aspects strongly suggest a diagnosis of CADASIL. Systematic screening of the NOTCH3 gene found a pathogenic mutation in 69.5% (32/46). Clinical and MRI features (except temporal lobe involvement) are not so different between our mutated and non-mutated patients (Pantoni et al., 2010; Pescini et al., 2012). These results imply that the NOTCH3 gene should be sequenced in all patients under 50 years of age with vascular white matter involvement and in older patients in the absence of atherosclerosis.

We found seven patients with COL4A1 gene mutation (13%). Diagnosis was first suggested by the presence of
<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of patients</th>
<th>Sex ratio (M/F)</th>
<th>Familial history</th>
<th>Age at onset (range)</th>
<th>Main neurological findings</th>
<th>Specific MRI finding</th>
<th>Other clinical findings</th>
<th>Mutated gene(s)</th>
</tr>
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<tbody>
<tr>
<td>FXTAS</td>
<td>4</td>
<td>4/0</td>
<td>2/4</td>
<td>64.5 (52–75)</td>
<td>Cerebellar ataxia (4), tremor (3),</td>
<td>MCP HI (4), cerebellar HI (4) and atrophy (4), CC involvement (3)</td>
<td>–</td>
<td>FMRI</td>
</tr>
<tr>
<td>Hereditary spastic paraplegia</td>
<td>4</td>
<td>3/1</td>
<td>1/4 (AR)</td>
<td>26 (17–39)</td>
<td>Spastic paraparesis (4), cognitive (2),</td>
<td>Hypomyelination (4), corpus callosum atrophy (2)</td>
<td>–</td>
<td>Spatacsin (SPG11) (2), KIF5A (1), PLP1 (1)</td>
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<tr>
<td>ADLD</td>
<td>2</td>
<td>1/1</td>
<td>2/2</td>
<td>46.5 (45–48)</td>
<td>Cerebellar ataxia and tremor (2), cognitive (2), pyramidal (1)</td>
<td>MCP (2), pons (2), pyramidal tract (2),</td>
<td>–</td>
<td>LMNB1</td>
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<td>LBSL</td>
<td>2</td>
<td>0/2</td>
<td>1/2 (AR)</td>
<td>21 (20–22)</td>
<td>Pyramidal (2), cerebellar (1)</td>
<td>MCP (2), cerebellar atrophy (2), pons and spinal cord HI (2)</td>
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<td>DARS2</td>
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<tr>
<td>Oculo-dentodigital syndrome</td>
<td>2</td>
<td>0/2</td>
<td>1/2 (AD)</td>
<td>24 (16–32)</td>
<td></td>
<td>Hypomyelination (2)</td>
<td>Syndactilia (2)</td>
<td>GA1</td>
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<tr>
<td>CMTX</td>
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<td>1/0</td>
<td>no</td>
<td>16</td>
<td>Symptomatic peripheral neuropathy</td>
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<td>–</td>
<td>Connexin 32 (GJB1)</td>
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<td>3</td>
<td>1/2</td>
<td>2/3 (mat)</td>
<td>45</td>
<td>Cerebellar ataxia (3), seizures (1), axonal neuropathy (1)</td>
<td>Cerebellar atrophy (3)</td>
<td>Deafness (2), optic atrophy (1)</td>
<td>Point mutation: – 3243A &gt; G, – 12258C &gt; A; multiple deletions</td>
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<tr>
<td>HDLS</td>
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<td>0/2</td>
<td>1/2 (AD)</td>
<td>45</td>
<td>Cognitive (2), dystonia (1)</td>
<td>Frontal predominance and atrophy</td>
<td>Secondary amenorhoea</td>
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<tr>
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<td>no</td>
<td>46</td>
<td>Pyramidal and cognitive</td>
<td>Pons and medullary HI, vermis, medullary and spinal cord atrophy</td>
<td>–</td>
<td>GBE1</td>
</tr>
</tbody>
</table>

AD = autosomal dominant; ADLD = adult-onset autosomal dominant leukodystrophy; APBD = adult-onset polyglucosan body disease; AR = autosomal recessive; CC = Corpus Callosum; CMTX = X-linked Charcot-Marie-Tooth disease; FXTAS = fragile X-associated tremor ataxia syndrome; HDLS = hereditary diffuse leukoencephalopathy with axonal spheroids; HI = Hyperintensities; mat = maternal; MCP = middle cerebellar peduncle hyperintensities.
classic phenotypes including porencephalic cavities (but inconstant), calcifications and microbleeds (Vahedi and Alamowitch, 2011). Contrary to CADASIL patients, temporal lobe was always spared. Familial history and extra neurological signs were inconstant.

Cavitary leukoencephalopathies are radiologically defined by the association of a diffuse leukoencephalopathy and hypointensities within large areas of demyelination on FLAIR sequences. This aspect evokes first the diagnosis of childhood ataxia with CNS hypomyelination (Labauge et al., 2009), which was asserted in 76% (13/17) of these patients. This high rate of diagnosis is significant in spite of similar MRI in EIF2B mutated and non-mutated patients. Consequently, sequencing of EIF2B genes is justified in every patient with cavitary leukoencephalopathy. Importantly, the recurrent R113H mutation in the EIF2B5 gene is found in most of the cases (Labauge et al., 2009; Carra-Dalliere et al., 2011).

In Group 3, the systematic metabolic screening allowed a diagnosis of inborn error of metabolism in 28% of the patients (23/82), confirmed by molecular analysis. Similar to Müller vom Haen et al. (2014), we found only five diseases: X-linked adrenoleukodystrophy, cerebrotendinous xanthomatosis, Krabbe disease, metachromatic leukodystrophy and α-mannosidosis. In a series of 122 infantile leukodystrophies, the most common diagnoses were metachromatic leukodystrophy and X-linked adrenoleukodystrophy (Bonkowsky et al., 2010). In our series, X-linked adrenoleukodystrophy was by far the most frequent metabolic diagnosis (n = 11/82, 13.5%). Brain MRI shows various patterns from subtle T2-weighted hyperintensities of the corticospinal tracts to more extensive white matter lesions, sometimes with gadolinium enhancement (Carra-Dalliere et al., 2013). Cerebrotendinous xanthomatosis (with characteristic cerebellar white matter and dentate nuclei hyperintensities) and Krabbe disease were found in five and three patients, respectively. These two diseases have been mainly described as paediatric diseases, with increasing publications of adult-onset patients (Debs et al., 2013; Lionnet et al., 2014). Our results suggest that every patient with an adult-onset leukoencephalopathy without vascular or cavitary pattern should have a systematic metabolic screening to search at least four diseases: X-linked adrenoleukodystrophy, cerebrotendinous xanthomatosis, Krabbe disease and metachromatic leukodystrophy. In case of negative screening, all other inborn errors of metabolism should then be searched.

In Group 3, 21 patients had a diagnosis confirmed by direct molecular screening or pathological analysis (biochemical screening was normal in all). The great number of possible diagnoses requires a careful analysis of brain MRI (Schiffmann and van der Knaap, 2009) (Table 1).
Conclusion

In conclusion, our series represents the first adult-onset leukoencephalopathy cohort including 154 patients with symmetrical white matter hyperintensities and age of onset > 16 years, of whom 64% finally have a diagnosis. In spite of the retrospective analysis and the possible inclusion of some patients with acquired diseases, this series gives an overview of the global burden of inherited adult-onset white matter diseases. Finally, our classification, based on an easy-to-use MRI pattern analysis, proposes a new decision algorithm in the management of adult-onset leukoencephalopathies.

References


