Original Article

Posterior fossa imaging in 158 children with ataxia

Apport de l’IRM dans les syndromes cérébelleux chez l’enfant : à propos de 158 cas

Introduction

The etiological characterization of cerebellar ataxia in children is still based on clinical classification and remains rare and difficult despite the availability of recently developed genetic and biochemical techniques. At least, 30 diagnosis are possible from clastic lesions to genetic or metabolic diseases [1]. The clinical symptoms and signs are generally non-specific and overlapping. Although insufficient, the clinical course is important to differentiate progressive degenerative syndrome from complex midbrain and hindbrain stable malformation.

Several genes implicated in cerebellar ataxia have been recently described in metabolic and degenerative disorders (CABC1 in quinone deficiency, FRAXA in Freidreich ataxia, SCAs in spinocerebellar ataxia, AOA1, AOA2 in ataxia associated with ocular apraxia) as well as in developmental diseases as in the spectrum of Joubert syndrome (INPP5E(JBS1) AHI1(JBS3), NPHP1 (JBS5-4), CEP290 (JBS5), TMEM67 (JBS6), RPGRIP1L(JBS7), ARL13B (JBS8), CC2D2A (JBS9) and very recently OFD1(JBS10) [2—10]. Finally, several genes has been recently identified in pontocerebellar hypoplasia [11].

In the two last years, genetic studies for cerebellar diseases are often based on clinical phenotypic identification of homogeneous groups of patients in the hope that they will possess a similar genetic condition. Similar genes mutations have been shown to be associated with similar brain MRI features, then cerebellar anomalies such as vermic dysgenesis with cleft were found to be associated with OPHN1 mutation [12] or molar tooth malformation with CEP290 or RPGRIP1L mutations [5,7].

In the same line (similar MRI/similar diagnosis), we report here, our multidisciplinary (pediatric neuroradiologist, neuropediatrician, genetician) experiences in the study of the brain MRIs of a cohort of 158 cerebellar ataxic children. Gathering together clinical data, detailed neurological examination, brain and cerebellar associated abnormalities as well as genetic testing findings, helps to build this algorithm using defined MRI-homogeneous groups of ataxic children. Seven groups of anatomical cerebellar abnormality were proposed, and were confronted to the biochemical and/or genetic results. The aim of this study, using a multidisciplinary approach of pediatric cerebellar ataxias, is to increase the diagnosis efficiency using a new cerebellar MR algorithm.

Methods

Clinical inclusion criteria

One hundred and fifty-eight patients were enrolled in a study-based upon the clinical findings of ataxia, or cerebellar signs such as oculomotor abnormalities, truncal ataxia and head movements if the child was too young or too severely handicapped. All children (mean age 5.0years) were included in the study if ataxia had begun during paediatric age (15 years of age). Patients were referred from the departments of pediatric neurology, genetics, metabolism or ophthalmology of Necker Enfants Malades Hospital, Paris, France.

MRI studies were performed during sleep induced by premedication (5 mg/kg of sodium pentobarbital) if necessary to obtain immobility during scans.

Clinical exclusion criteria

Patients were excluded if ataxia occurred after the age of 15 years old or if they presented with posterior fossa tumors, signs of acute infectious disease, acute stroke or hematomas. Dandy Walker malformations were not included in the series because ataxia is not a feature of the clinical presentation. We excluded from our series the Freidreich ataxia patients because the diagnosis was based on the clinical and biological data or familial history before the MRI. We excluded all children with supratentorial abnormalities on MRI because the etiologies of the diseases are completely different (for example O-glycosylation or mutation in genes of tubulin [13]).

Clinical and neurophysiological investigations

Clinical investigations included collecting history and a physical examination that consisted of cognitive, neurological and dysmorphic evaluations. Neurophysiologic investigations including electroencephalogram, electromyogram, nerve conduction studies, auditory evoked potentials, electroretinogramme were performed if indicated.
Brain imaging

MRI acquisition
All ataxic children received an anatomical MRI. The MRI examination consisted of sagittal spin echo (SE) T1, axial fast SE (FSE) T2 and coronal fluid-attenuated inversion recovery (FLAIR) images. In some cases supplemental imaging sequences were obtained including 3D fast spoiled gradient echo (FSPGR), T2*. H1 magnetic resonance spectroscopy MRS monovoxel spectroscopy was most commonly performed using PRESS TR = 1500 and TE = 144 (voxel 2 cm × 2 cm × 2 cm). Spectroscopies were performed in the dentate nucleus of the cerebellum or in the putamen. Brain MRI was always performed without injection of contrast.

Cerebellar MRI Algorithm
A data base was built including clinical findings, genetic, metabolic data and brain MRI. Based on visual inspection, patients were classified into seven imaging groups in order to construct radiologically-homogeneous subgroups. They were assigned to seven broad categories based upon the MRI appearance of the posterior fossa.

Cerebellar hypoplasia. Small and normally organized cerebellum (dwarf or tiny cerebellum). These abnormalities constituted three subgroups.

Pontocerebellar hypoplasia. Global brainstem hypoplasia associated with cerebellar hypoplasia (Fig. 1A and B). The hemispheres had a flattened shape on coronal slices, which reflected the hypoplasia of the hemispheres.

Abnormal dorsal brainstem associated with cerebellar hypoplasia. Abnormal portion of the brainstem (PTCD: pontocerebellar cap dysplasia) (Fig. 1C and D).

Normal Brainstem. Small vermis but the hemispheres could be small but were never flattened.

Vermian dysgenesis (molar tooth). The dysgenesis was always localized in the superior vermicular structures indicating a disorganization of the superior vermis on axial MRI (Fig. 2). The “molar tooth sign” associated the superior vermicular dysgenesis and abnormally-oriented (more horizontal than normal) and thickened cerebellar peduncles.

Hemispheric cerebellar dysgenesis. Disorganization of the anatomical cerebellar hemispheres. The neural cerebellar hemispheric structures were recognizably present and complete, but the organization was abnormal (Fig. 3). The vermicular structures and the brainstem were nor-

Figure 1  Cerebellar hypoplasia. Pontocerebellar hypoplasia: sagittal T1 weighted image (A) shows that this group included patients with a small, but normally organized cerebellum. Both the vermis and the two hemispheres were smaller than those of normal cerebellum. The brainstem was also hypoplastic. Coronal FLAIR (B) shows that the hemispheres had a flattened shape, which reflected the hypoplasia of the hemispheres; Abnormal dorsal brainstem associated with cerebellar hypoplasia: sagittal T2 weighted image (C) shows that this group included patients with a small, but normally organized cerebellum. The brainstem was always hypoplastic with an abnormal dorsal portion. Coronal T2 (D) shows an hypoplasia of the cerebellar hemispheres.
Vermian dysgenesis (molar tooth sign). Axial MRI (A and C) shows a dysgenesis localized in the superior vermian structures indicating a disorganization of the superior vermis compared to normal control (B); the figure C also shows the "molar tooth sign" which associated the superior vermian dysgenesis and abnormally-oriented and thickened cerebellar peduncles. Sagittal MRI (D) shows a dilatation of the fourth ventricle.

Unilateral hemispheric cerebellar atrophy. This atrophy was associated with a localized hypersignal on T2 and FLAIR sequences in the sub-cortical structures suggesting a gliosis (Fig. 4).

Global cerebellar atrophy. The cerebellum had normal organization, normally constructed with three lobes, but the fissures and sulci were wider and deeper than those seen in normal subjects. Two subgroups were defined:

- major cerebellar atrophy. In these extreme cases, atrophy was so severe that the size of the vermis was extremely small (Fig. 5A and B). Progression of atrophy were demonstrated with two MRIs at two separate times;

Hemispheric cerebellar dysgenesis. Sagittal MRI (A) shows that the vermian structures were not disorganized; the brainstem was always normal. Axial MRI (B) and Coronal (C) show a disorganization of the left anatomical cerebellar hemisphere.
Figure 4  Hemispheric cerebellar atrophy. Sagittal T1 MRI (A) shows a dilatation of the fourth ventricle. Axial T1 MRI (B) and coronal FLAIR (C) show a left cerebellar hemispheric atrophy. This atrophy was associated with a hypersignal on coronal FLAIR sequences in the subcortical structures (C). A cleft of the hemispheric cerebellar structure was seen on axial T1 (B).

- minor atrophy of the cerebellum. In this group, the cerebellar atrophy was characterized by exacerbation of vermian foliation without reduced volume of the entire cerebellum without progressive atrophy (Fig. 5C and D).

Cerebellar signal abnormalities. Abnormal hyperintensities on T2 or FLAIR images in the vermis, dentate nuclei or cerebellar hemispheres of the cerebellum (Fig. 6A and B). The brainstem was always normal.

Normal cerebellar MRI. The size, shape and signal appearances of the cerebellum and brainstem were normal (Fig. 7).

Biochemical and genetical investigations depending of algorithm

From this algorithm, we considered two mechanism involving posterior fossa diseases (Fig. 8):

Figure 5  Global cerebellar atrophy. The cerebellum had normal organization, normally constructed with three lobes, but the fissures and sulci were wider and deeper than those seen in normal subjects. Major cerebellar atrophy (A and B): sagittal MRI (A) and coronal MRI (B) show that atrophy was so severe that the size of the vermis was extremely small; Minor atrophy of the cerebellum (C and D): sagittal MRI (C) and coronal MRI (D) show that the cerebellar atrophy was characterized by exacerbation of vermian foliation without reduced volume of the entire cerebellum.
Posterior fossa imaging in 158 children with ataxia

Figure 6  Cerebellar signal abnormalities. Coronal FLAIR image shows diffuse hyperintensities in the vermis and dentate nuclei (A, patient 1). Coronal FLAIR image on patient 2, only shows abnormal hyperintensities in the dentate nuclei (B, patient 2).

Figure 7  Normal cerebellar MRI. Coronal MRI (A) and sagittal MRI (B) show a normal size, shape and signal appearances of the cerebellum. The brainstem is normal.

- developmental or malformative disorder and;
- clastic or metabolic disorder.

The malformative disorder included three groups as cerebellar hypoplasia, vermian dysgenesis and hemispheric cerebellar dysgenesis. High resolution karyotype and eventually CGH array was performed in hemispheric cerebellar dysgenesis, even if they had no dysmorphic features. Specific genetic screening was performed when indicated in cases of Joubert related syndromes (vermian dysgenesis) as AHI1, NPHP1, CEP290, RPRGIP1L and TMEM67 genes. In cases of cerebellar hypoplasia TSEN54, TSEN2, TSEN34 and CASK are in course [11].

The clastic or metabolic disorder included: unilateral hemispheric cerebellar atrophy, global cerebellar atrophy, cerebellar signal abnormalities and normal cerebellar MRI. These patients had extensive biochemical screening with complete blood count and blood smear (detection of acanthocytes and vacuolated lymphocytes), liver function tests, creatine kinase and LDH, cholesterol, triglycerides and lipoprotein electrophoresis, cholestanol, creatinine and urinary osmolarity, albumin, α-fetoprotein, vitamin E and apolipoprotein B, immunoglobulins and IgG sub-classes, blood lactate, pyruvate, and amino acids, urinary organic acids chromatography, carnitine, isoelectric focusing of transferrin, very long chain fatty acid and phytanic acid, lysosomal enzymes, urinary sugar and oligosaccharides. The Bratton-Marshall test was performed on urine as a screening method for adenylosuccinase deficiency. Skeletal muscle and liver biopsies with histology examination and assay of respiratory chain enzymes in isolated mitochondria were performed [14] when mitochondrial respiratory chain deficiency was suspected.

Results (see MR cerebellar algorithm).

General results

Based on anatomical MR cerebellar algorithm, 15 children were classified in cerebellar hypoplasia group, 27 children were classified in vermian dysgenesis group, six children in hemispheric cerebellar dysgenesis group, five children in hemispheric unilateral atrophy group, 84 children in global cerebellar atrophy group, eleven children in signal abnormalities group and ten children in the normal MRI group. A specific molecular genetic or biochemical diagnosis was obtained in 56 of 158 children based on anatomical MR cerebellar algorithm (Fig. 8).
We present each group in detail

**Hypoplasia of the cerebellum: n = 15**

*Pontocerebellar hypoplasia (n = 10; mean age 23 months).*

This group included children with very similar clinical presentation characterized by microcephaly which was present in all ten patients associated with severe mental retardation (10 of 10), extrapyramidal signs (10 of 10) with movement disorders, visual impairment (10 of 10), trigonocerebral (one of 10). During the neonatal period two of 11 patients died due to respiratory distress. They did not have retinopathy or motoneuron involvement. Of these, one patient was found to harbor mutation p.A307S; c.919G > T in the TSEN54 gene, recently involved in PCHZ [15]. The other nine are still under screening for TSEN54, TSEN2, TSEN34 and CASK [11].

**Abnormal dorsal brainstem associated with cerebellar hypoplasia (n = 2; mean age 54 months).** This group presented with clinical signs of cranial nerve dysfunction, particularly anesthesia of the trigeminal nerve territory. They had pyramidal signs, dysmetria and ataxic trunk, and mild mental retardation with a normal head circumference. The asymmetrical involvement of cranial nerves (VII, VIII, VI and V) seemed to be specific to the so-called “pontine tegmental cap dysplasia” by the authors [16].

**Normal Brainstem (n = 3; mean age 72 months).** The clinical features were less specific with ataxia and variable mental retardation. In this group, no specific genetic nor biochemical diagnosis was found.

**Vermian dysgenesis (molar tooth): n = 27; mean age 50 months**

Eight of twenty-seven patients had a specific genetic diagnosis. Three patients had mutations in the *CEP290* gene; *RPGRIP1L* was involved in one patient; *AHI1* was involved in two patients and *TMEM67* was involved in two patients. These patients were partially described in a previous study [17]. Hypotonia, abnormal eye movements and early developmental delay were consistent features in all patients, but variable severity of developmental delay, ataxia, hypotonia and apnea were also found. Other clinical features included polydactyly, renal hypoplasia, liver cholestasis, retinopathy and ventricular septal defect were observed occasionally (see Table 1). Nineteen of 27 patients had still not genetic diagnosis despite extensive investigations. Neither clinical nor radiological differences have been found between the genetically characterized group and this one. Seventeen of 19 patients had mild to severe mental retardation, and ocular apraxia was noted in six of 19 cases. No kidney lesions were found, except one case of renal hypoplasia, and no dysmorphic features were found, except polydactyly in two sisters.

**Hemispheric unilateral cerebellar atrophy (n = 5; mean age 40 months)**

Unilateral hemispheric atrophy associated with hemispheric cleft in three cases might correspond to a destruction of the parenchyma that could reflect a clastic lesion. In all cases, the fourth ventricle was enlarged. One child in this group had a history of prenatal injury. This cleft could be similar to the unilateral supratentorial cleft (schizencephaly) known to be related to vascular injury [18]. The clinical data supported this hypothesis. Indeed, all patients presented with psychomotor delay, including mild mental retardation, hemiparesia with unilateral dysmetria and dysarthria, and all of them had strabismus without ocular apraxia.

**Global cerebellar atrophy (n = 84, mean age 74 months)**

Sixty patients had a major cerebellar atrophy and 24 patients had a minor cerebellar atrophy. A specific biochemical diagnosis was performed for most patients (40 of 60) with a major atrophy, but no diagnosis was made in the group of minor atrophy.

Subgroup with major atrophy (n = 60, mean age 56 months): Forty-one of 60 (68%) patients with a major cerebellar atrophy suffered from a metabolic disease.

Twenty-one CDG Ia (congenital disorders of glycosylation type 1a) with sequencing of the *PMM2* gene, was diagnosed. Of the 21 with CDG Ia, non-progressive mental retardation (mild to severe), strabismus, retinopathy and late onset neuropathy were found. No correlation between the cerebellar atrophy and the severity of mental retardation was observed.

Eighteen mitochondrial respiratory chain deficiencies (RCD) of one or more mitochondrial complexes were diagnosed in the liver or skeletal muscle biopsies. Recessive mutations in the *POLG* gene were identified in one patient with a liver mitochondrial depletion. Recessive mutations in the *CABC1* gene [19] were found in five patients. Different/multiple enzymatic deficiency were observed in twelve children (complex IV deficiency in muscle in one child, complex V deficiency in muscle in one child, multiple enzymatic deficiency in muscle in one child; Complex IV deficiency in liver in four children and no deficiency in muscle in five children). Progressive encephalopathy, cerebellar ataxia and dysmetria, neuropathy (sensitive and axonale), retinopathy, recurrent events of neurological regression and status epilepticus were frequent. Cerebral spectroscopy was thus useful to search for a peak of lactate in posterior fossa in case of energetic disease [20].

One very early infantile neuroaxonal dystrophy (INAD) was confirmed with two mutations in the *PLA2G6* gene.

In ten patients without diagnosis and presenting with ocular apraxia associated with ataxia, *AOA1* genes mutations have not been found. No mutation in *SCA7* gene has been found in two familial cases.

**Subgroup with minor atrophy n = 24; mean age: 100 months**

All these patients had a very stable clinical presentation in time. These patients have been found to have delayed cognitive and motor development, a progressive improvement of coordination and ataxia with increasing age, but...
Table 1  Clinical features of eight patients in the spectrum of Joubert syndrome with molecular genetic etiology and whose MRI examinations demonstrated vermian dysgenesis (molar tooth sign).

<table>
<thead>
<tr>
<th>Case</th>
<th>Mental retardation</th>
<th>Hypotonia/Truncal ataxia</th>
<th>Abnormal eye movements</th>
<th>Retinopathy</th>
<th>Kidney</th>
<th>Gene</th>
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<tr>
<td>Case 1</td>
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<td>JBS5 = CEP290 = NPHP6</td>
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<td>Case 2</td>
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<td>-</td>
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<td>JBS5 = CEP290 = NPHP6</td>
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<tr>
<td>Case 3</td>
<td>+ +</td>
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<td>-</td>
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<td>JBS5 = CEP290 = NPHP6</td>
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<tr>
<td>Case 4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<td>JBS3 = AHI1</td>
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<td>Case 5</td>
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<tr>
<td>Case 6</td>
<td>+</td>
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<td>+</td>
<td>JBS7 = RPGRIP1L = NPHP8</td>
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<td>Case 7</td>
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<td>-</td>
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<td>JBS6 = MKS3 = TEMEM67</td>
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<tr>
<td>Case 8</td>
<td>+ +</td>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>JBS6 = MKS3 = TEMEM67</td>
</tr>
</tbody>
</table>

Figure 8  MR cerebellar Algorithm in 158 ataxic children with no supratentorial abnormalities.

language disorder persisted on verbal performances. All of them had mild pyramidal or extra pyramidal signs without ocular apraxia, dysmetry or dysarthria. Some of them were believed to have a cerebral palsy. Six patients had non-progressive atrophy confirmed at two different MRIs, and eighteen patients had only one cerebral MRI. They all had an extensive investigation, including skeletal muscular biopsy in two patients. In this group, we found no diagnosis, but there were five familial cases.

Signal cerebellar abnormalities (n = 11; mean age 89 months)
Among the eleven patients with signal anomalies of the cerebellum, including diffuse cerebellar hyperintensity (n = 6) and dentate nucleus signal hyperintensity (n = 5), six patients had a specific diagnosis. Five patients had a respiratory chain deficiency (Complex IV deficiency in muscle (one case), Complex V deficiency in muscle (one case), Complex IV deficiency in muscle and liver (one case) and no deficiency in muscle (two cases). In two patients with mitochondrial respiratory chain deficiency, a peak of lactate was observed in the cerebellum at 1H MRS [20]. Sulphite oxidase deficiency was found in one patient. Five patients had no specific diagnosis identified despite an extensive investigation.

Normal cerebellar MRI (n = 10; 63 months)
Ten patients with clinical ataxia had normal cerebral MRI. All patients had moderate mental retardation: they lacked language skills but were ambulatory. Half of the cases had dysmorphic features. No diagnosis has been established in this group despite extensive investigations.

Discussion
Based on seven subgroups of homogenous cerebellar radiological imaging, we described the malformative or metabolic diagnosis in 158 ataxic children (Fig. 8). In this series, 56 of 158 children received specific diagnoses. This MR algorithm, applicable only in patients with nor-
mal cerebrum, permitted easy separations of patients who are likely to have metabolic diseases (major cerebellar atrophy or signal abnormality) from those with malformative disease (vermian dysgenesis or cerebellar hypoplasia).

In the group of dysgenesis of the vermis, a specific genetic diagnosis was obtained in eight of 27 patients. In the group of pontocerebellar hypoplasia, a specific genetic diagnosis was obtained in one patient. In the group of cerebellar major atrophy and signal abnormalities, a specific biochemical diagnosis was obtained in 46 of 71. In the other groups, hemispheric cerebellar dysgenesis, minor global atrophy and normal MRI, no specific diagnosis was found for any patients. In the group of unilateral hemispheric atrophy, we hypothesize a clastic prenatal injury.

The patients whose MRI examinations demonstrated vermian dysgenesis included those who are most likely to establish a specific malformative diagnosis. The vermian dysgenesis group, corresponding to 17% of our study’s patients, had a molecular genetic etiology in eight of 27 patients. All of the mutated genes (AHI1, TMEM67, CEP290 and RPGRIP1L) are involved in ciliary function [2]. A cilia dysfunction is associated with diverse human disorders. In brain, it has recently been shown that primary cilia is essential for Shh-dependent expansion of cerebellar progenitors cells (suggesting that cerebellar abnormalities observed in Joubert could be explained by defects in Shh-induced cerebellar progenitor cells expansion [21]. In these cases, metabolic investigations are not necessary.

Conversely, the patients whose initial ‘endophenotypic’ (referring to similar MRI characteristics) categorization was major cerebellar atrophy or cerebellar signal abnormality demonstrated metabolic etiologies. The metabolic disorders were mitochondrial respiratory chain deficiency (RCD) in 30% of cases (18 of 60), CDG la in 36% of cases (21 of 60), one very early infantile neuroaxonale dystrophy (INAD) with two mutations in the PLA2G6 gene and sulphite oxidase deficiency in one case. Therefore, if major cerebellar atrophy or cerebellar signal abnormalities are identified on cerebral MRI, then the metabolic workup is quite useful, which confirmed the presence of respiratory chain abnormalities or glycosylation anomalies in the majority of cases (44 of 71 patients; 60% of cases). Cerebral spectroscopy is thus useful to search for a peak of lactate in posterior fossa in case of energetic disease. Signal abnormalities in cerebellum are known to be present in few metabolic disorders. For example, in Succinic semialdehyde dehydrogenase deficiency, a rare disorder of the degradation pathway of gamma-aminobutyric acid, MRI typically reveals increased T2-weighted signal of the cerebellar dentate nucleus associated with variable involvement of white matter and the globus pallidus [22]. In Refsum syndrome related to a peroxisomal disorder with high phytic acid level, the first sign on imaging of the disease is an isolated hypersignal in T2 weighted images of cerebellar dentate nuclei later associated with abnormalities in subthalamic nucleus and globus pallidus [23]. In the same way, in cerebrotendinosis xanthomatosis, clinical features may vary greatly in term of age of beginning and skin lesions but all the radiological studies have suggested that the bilateral abnormality of the dentate nuclei also could be typical [24]. We had investigated our patients with cerebellar signal abnormalities for these metabolic disorders without any positive result, probably due to the fact that we have excluded patients with supratentorial anomalies.

Thus, we found four main homogenous radiological subgroups (cerebellar hypoplasia, vermian dysgenesis, major atrophy and signal abnormalities) in which the MR cerebellar algorithm could be helpful. To go further with the decision, a genotype-phenotype correlation is suggested.
for the vermis dysgeneisis subgroup. Based on our experience and the literature [2], in the case of no other clinical signs is associated to the vermis defect, the search for AHI1 gene mutations is first recommended and after MKS6 = CC2D2A = JB59 and INPP5E = JB51 could be done. In the case of renal signs are present, the NPHP1 gene deletion could be searched on first line, or if the patient has in addition a retinopathy, CEP290 and/or RGPRIPL1 genes mutations are more likely search (see Fig. 9).

For the two other radiologically-homogenous subgroups in which a metabolic diagnosis could be done (major atrophy or signal abnormalities), extensive metabolic investigations are necessary with first line N-glycosylation and 1-H-MRS spectroscopy of cerebellum before investigating mitochondrial disorder.

In the group of unilateral hemispheric atrophy, one child had a history of clastic prenatal injury. The radiological findings observed as unilateral asymmetrical lesion and cerebellar cleft looked like the supratentorial cleft seen after ischemic/hypoxic prenatal damage at the supratentorial level. This MR aspect of the cerebellum has been previously described in prenatal investigations [25] and was confirmed by neuropathological study as ischemic lesion [26] and also recently described by Poretti et al. [18]. In the study of Sharony, no children had supratentorial abnormalities, their vermis structures were normally organized, so they all had the same moderate clinical signs. This group constituted a homogeneous clinical and radiological subgroup with a better prognosis. We may suppose that this group of patients (in which the vermis structures are not disorganized) have all the correct connections between the vermis and the supratentorial structures.

In the current cohort, 65% of children (102 of 158) with cerebellar ataxia remained undiagnosed. However, using the MR algorithm we have identified four other quite interesting radiological and clinical homogeneous subgroups of patients. The first subgroup of pontocerebellar hypoplasia presented the same clinical spectrum including neonatal microcephaly, severe encephalopathy with pyramidal signs associated with early movements disorders (dyskinetic and choreic). In this group, we have found only one patient with a mutation in the TSEN54 gene, recently involved by Barth et al. This MR aspect of the cerebellar hemisphere in children hindered verbal performance. Some of them were believed to be cerebral palsy. This group of non-progressive ataxia with cognitive impairment may be considered as genetic with recurrence due to familial risk since there are five familial cases in our study as previously described [27]. The last radiological subgroup without diagnosis consists of those with normal MRI with clinical ataxia, moderate mental retardation and dysmorphic feature. In these homogenous radiological and clinical subgroups, neither multiplex nor consanguineous families were found except one. Therefore, a genetic cartography approach to identify a genetic aetiology may be based on a candidate gene approach or a high resolution CGH array.

Since diffusion tensor imaging (DTI) appears to be a promising imaging method for characterizing anatomical disruptions that occur in cerebellar diseases [28], further cerebellar input and output fiber tracking studies could have a positive impact for more accurate radiological classification of cerebellar disorder leading to better etiological diagnosis. Thus, a prospective MRI study, with 3D FSPGR T1, axial T2, coronal FLAIR, cerebellar H1 MRS and DTI sequences, applied in the different cerebellar subgroups could be helpful in the understanding of cerebellar ataxia in children.

**Conclusion**

The "imaging phenotype" or "endophenotype" (referring to similar MRI characteristics) is useful as criteria for a morphologic radiological classification of the cerebellum. Previous approaches of the classifications of posterior fossa malformations were based on knowledge of posterior fossa embryology. However, these classifications although extremely important to understand the origin of cerebellar malformations are less useful to make a precise diagnosis in the clinical setting of pediatric ataxia. We propose here, using a multidisciplinary approach, a MRI cerebellar algorithm to guide genetic or metabolic investigations in order to increase the diagnosis efficiency. We suggest that this MR cerebellar algorithm "might be used" to characterize similar clinico-radiological phenotypes in the hope of identifying new diseases using innovative imaging or new genetic approach.

**Conflicts of interest**

None.

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**References**


