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REVIEW

Role of neuroimaging in the diagnosis of hereditary cerebellar ataxias in childhood

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Summary Hereditary ataxias are a heterogeneous group of neurodegenerative disorders, characterized by cerebellar ataxia as the main clinical feature, and a large spectrum of neurological-associated symptoms and possible multi-organ affection. Image-based approaches to hereditary ataxias in childhood have already been proposed. The aim of this review is to yield the main reports of neuroimaging patterns and diagnostic algorithms and compare them with the results from our study of 23 young patients addressed for ataxia, with subsequent genetic or metabolic diagnosis.

Abbreviations: A-T, ataxia-telangiectasia; AD, Alexander disease; CDG-Ia, congenital disorder of glycosylation type Ia; CMD1A, congenital muscular dystrophy type 1A; CS, Cockayne syndrome; FRDA, Friedreich ataxia; H-ABC, hypomyelination with atrophy of the basal ganglia and cerebellum; L-2-HGA, L-2-hydroxyglutaric aciduria; MSS, Marinesco—Sjögren syndrome; MLD, metachromatic leukodystrophy; MMA/HC cbIC, methylmalonic acidemia with homocystinuria cbIC; MNGIE, mitochondrial neurogastrointestinal encephalopathy syndrome; NCL, neuronal ceroid lipofuscinoses; PDHD, pyruvate dehydrogenase complex deficiency.

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Introduction

Hereditary ataxias are a heterogeneous group of neurodegenerative disorders, characterized by a cerebellar ataxia as the main clinical feature, associated with a large spectrum of neurological-associated symptoms and possible multiorgan affection. Ataxia results from dysfunction of the cerebellum and brainstem and/or its afferent or efferent tracts.

A first classification of hereditary ataxias was proposed in 1983 by Harding [1] based on their clinical and genetic features. In this classification, ataxias can be divided into two major groups according to the age of onset: autosomal recessive before 20 years, and autosomal dominant ataxias after 20 years of age [2]. More recently, Tirada et al. [3] has proposed a classification based on modes of inheritance: autosomal recessive, autosomal dominant, X-linked, mitochondrial, and incomplete penetrance.

If in the pediatric age group, the most common genetic cerebellar ataxia is autosomal recessive inheritance, autosomal dominant, X-linked and mitochondrial inheritance are possible [2,4].

Koenig [5] has used topographic and pathophysiologic criteria to categorize the rare autosomal recessive ataxias in three groups: sensory and spinocerebellar ataxias, cerebellar ataxias with sensory-motor polyneuropathy and purely cerebellar ataxias.

De Michele et al. [6] have proposed a pathogenetic classification in five pathogenic mechanisms: mitochondrial, metabolic, defective DNA repair, abnormal protein folding and degradation, and channelopathies.

Tirada et al. [3] and Palau et al. [7] categorized the autosomal recessive ataxias into four groups taking into account both genetic inheritance and clinical symptoms: degenerative, congenital, metabolic and disorders of DNA repair.

A specific genetic diagnosis of inherited ataxias is fundamental for an accurate counseling for the families. However, a genetic diagnosis is challenging, time-consuming, and costly; moreover, mutations in the same gene can give rise to different phenotypes, and similar phenotypes can derive from mutations in several genes. Furthermore, in about 40% of suspected hereditary ataxias, the underlying genetic defect is undetermined [8].

MR imaging is an excellent tool for describing brain abnormalities, especially of not only cerebellum but also of extracerebellar structures, to distinguish inherited ataxias from sporadic and acquired ataxias, to follow disease progression and to begin therapy as soon as possible for diseases that can be treated, and for differential diagnosis.

Therefore, an accurate clinical evaluation combined with an MR investigation remains crucial in the selection of further investigations, in particular genetic.

Some classifications and algorithms (Steinlin et al. [9], Poretti et al. [10], Boddaert et al. [11], Al-Maawali et al. [4], Vedolin et al. [12]) based on evaluation of cerebellar morphology, associated anomalies (involving white matter, basal ganglia, signal abnormalities of the cerebellum) on cerebral MRI and detailed neurological data have been proposed to guide the genetic and biochemical investigations allowing a diagnosis in 47% of cases in the larger cohort (300 cases) of Al-Maawali et al. [4] and in 35% of cases in the cohort (158 cases) of Boddaert [11].

We report our cohort of 23 young patients addressed for ataxia, with subsequent diagnosis, using an MRI-guided approach. The selected patients were affected by the following pathologies: Alexander disease (AD); ataxia-telangiectasia (AT); congenital disorder of glycosylation type Ia (CDG-Ia); Cockayne syndrome (CS); congenital muscular dystrophy type 1A-LAMA2 mutation (CMDIA); complex I of respiratory chain deficiency (complex I RD); complex IV of respiratory chain deficiency (complex IV RD); Friedreich ataxia (FA); hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC); Joubert syndrome (JSRD); L-2-hydroxyglutaric aciduria (L-2-HGA); Marinesco—Sjögren syndrome (MSS); metachromatic leukodystrophy (MLD); methylmalonic acidemia with homocystinuria cbIC (MMA/HC cbIC); mitochondrial neurogastrointestinal encephalopathy syndrome (MNGIE); neuronal ceroid lipofuscinoses (NCL); pyruvate dehydrogenase complex deficiency (PDHD); Wilson disease (WD). The MR imaging studies were performed with 1.5 T superconductive systems (Magnetom Aera, Siemens; Magnetom Avanto, Siemens), and with a 3 T superconductive system (Magnetom Skyra, Siemens).

On each scan, our qualitative evaluation was based on the following criteria (Table 1):

- cerebellar morphology: normal, focal or global cerebellar atrophy, hypoplasia/dysplasia, hypoplasia with atrophy;
- cerebellar signal: normal or T2/FLAIR hypersintensity of cortex, white matter and deep nuclei;
- brainstem morphology: normal or malformed, atrophy;
- brainstem signal: normal or T2 hyperintensity;
- supratentorial white matter signal: normal or T2/FLAIR hyperintensities on deep/periventricular, subcortical white matter or corticospinal tract;
- basal ganglia morphology: normal or atrophy;
- basal ganglia signal: normal or T2/T1 hyperintensities;
- search for calcifications;
- spinal cord morphology: normal or atrophy.

We focus our attention on autosomal recessive ataxias, mitochondrial disorders, and X-linked ataxias; since all our patients are children and young adults, we do not consider autosomal dominant ataxias [2], with the exception of Alexander disease, which is a rare case of autosomal dominant de novo mutation with early manifestation.

The aim of this review, along with the findings of major articles published on this subject, is to provide an image-guided diagnosis based firstly on the aspect of the cerebellum, which can be normal, globally or focally atrophic, hypoplasic, or malformed, and secondly on the possibly associated infra- and supratentorial anomalies (atrophy, malformation, signal anomalies). This approach could help the radiologist in identifying a type of ataxia, or a group of ataxias, according to MR and clinical data.

We selected five neuroimaging patterns of cerebellar abnormalities: no cerebellar atrophy, global cerebellar atrophy, focal cerebellar atrophy, cerebellar hypoplasia/dysplasia, and cerebellar hypoplasia-atrophy and tried to correlate them with an etiological diagnosis.