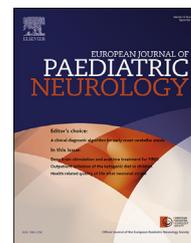




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## Original article

# A clinical diagnostic algorithm for early onset cerebellar ataxia



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## ABSTRACT

Early onset cerebellar Ataxia (EOAc) comprises a large group of rare heterogeneous disorders. Determination of the underlying etiology can be difficult given the broad differential diagnosis and the complexity of the genotype–phenotype relationships. This may change the diagnostic work-up into a time-consuming, costly and not always rewarding task. In this overview, the Childhood Ataxia and Cerebellar Group of the European Pediatric Neurology Society (CACG-EPNS) presents a diagnostic algorithm for EOAc patients. In seven consecutive steps, the algorithm leads the clinician through the diagnostic process, including EOA identification, application of the Inventory of Non-Ataxic Signs (INAS), consideration of the family history, neuro-imaging, laboratory investigations, genetic testing by array CGH and Next Generation Sequencing (NGS). In children with EOAc, this algorithm is intended to contribute to the diagnostic process and to allow uniform data entry in EOAc databases.

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## 1. Introduction

Early onset cerebellar ataxia (EOAc) comprises a large group of patients with rare disorders, manifesting symptomatic cerebellar ataxia before the age of 25 years. The estimated prevalence of EOA is 14.6 per 100,000 individuals.<sup>1–4</sup> Inheritance patterns can be classified as: autosomal recessive (most frequently), mitochondrial or autosomal dominant. In the latter, a strong family history (sometimes with misdiagnosed family members) is frequently present, but the mutation may also appear *de novo*. In contrast with adult onset ataxia, EOAc often presents with a wide variety of genotypes. This can be attributed to the neurological and non-neurological co-morbid features,<sup>5,6</sup> and to the variable disease course, which may range from stable to relentlessly progressive. Another aspect is that the initially dominating ataxic movement disorder phenotype may change over time. This is illustrated by young children suffering from the North Sea Progressive Myoclonus Epilepsy syndrome (caused by GOSR2 mutation), who initially present with ataxia as one of

the major symptoms at preschool age, which is progressively over-taken by myoclonus from about five years of age onwards.<sup>7</sup> Finally, it is important to realize that the heterogeneity of the EOAc phenotypes also reflects the heterogeneity of the underlying diseases. For instance, mitochondrial disorders involving both nuclear and mitochondrial genotypes can induce a large variety in clinical multisystem phenotypes, with proneness for ataxic features due to the energy demand of the cerebellar Purkinje cells.<sup>8</sup> To summarize, in children with EOAc, there is a large variety in genotypes with a heterogeneous phenotypic presentation. This can make the diagnostic work-up a challenging, time-consuming and expensive task, not only for the clinician but also for the children and their parents.

Over the past years, the availability of innovative Next Generation Sequencing (NGS) techniques<sup>9–11</sup> has enormously increased the diagnostic yield in pediatric neurologic disorders, such as epilepsy and childhood dystonia.<sup>10,12,13</sup> To optimize the diagnostic process in children with EOAc, the Childhood Ataxia and Cerebellar Group of the European

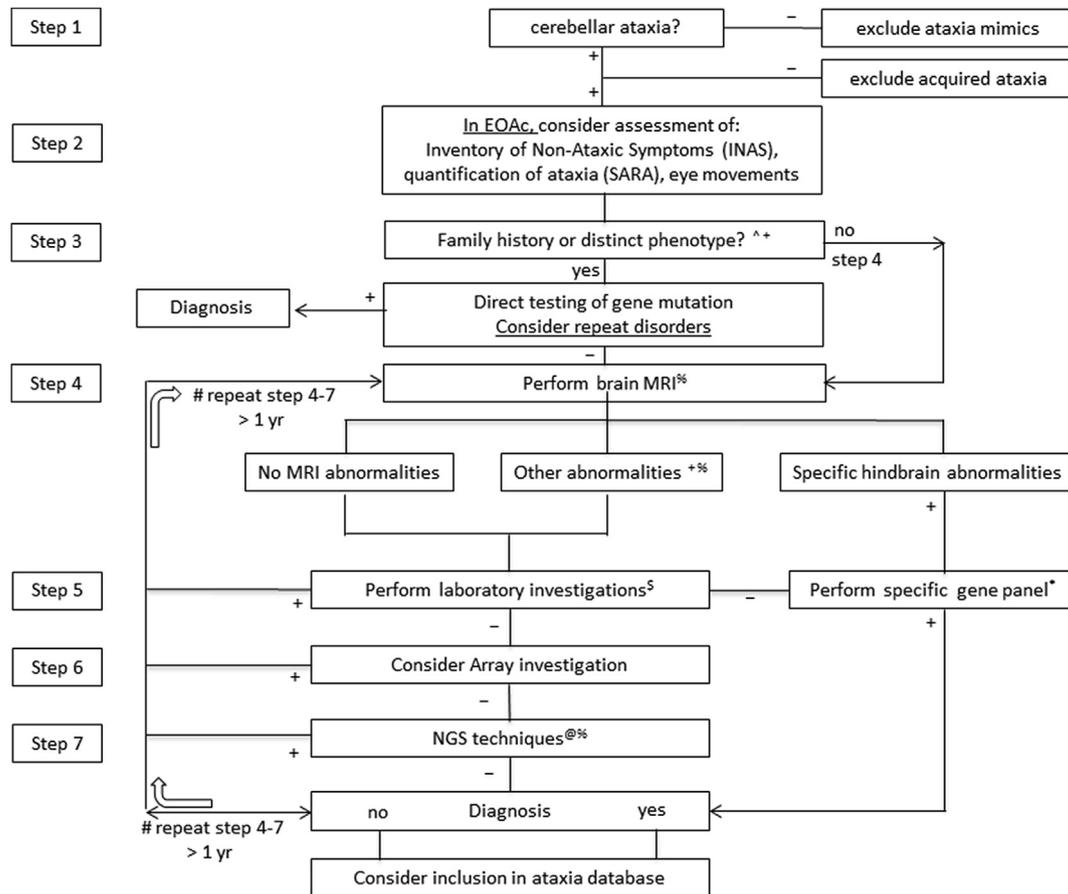
Paediatric Neurology Society (CACG-EPNS) has developed this diagnostic algorithm, based on the available literature as well as on expert opinions, expressed during the CACG-EPNS meetings over the last decade. After evaluation of the disease history, the present EOA algorithm will lead the clinician through the diagnostic process in seven consecutive steps (Fig. 1).

## 2. Clinical evaluation of the disease history

### 2.1. Step I: the clinical assessment of ataxia

The concept of “Early-Onset Ataxia” (EOA) refers to a heterogeneous group of diseases, mostly of genetic and/or metabolic origin, initiating before 25 years of age. In this algorithm, we focus on the detection of EOA by underlying cerebellar

etiology (EOAc). Cerebellar ataxia is characterized by the loss of smooth, goal directed, intended movements, after exclusion of other causes such as weakness and/or sensory disturbances.<sup>14</sup> In the newborn with absent voluntary movements, disturbed cerebellar function is often expressed by a stable or (slowly) progressive disease presentation with hypotonia, hypo-activity and oculomotor abnormalities.<sup>15</sup> This is illustrated by neonates with pontocerebellar hypoplasia type 2 who present with low muscle tone and jitteriness. Apart from uncoordinated sucking and swallowing behavior, clear ataxic features are mostly invisible due to the absence of goal directed movements.<sup>16</sup> After the neonatal period, when the child starts to develop voluntary goal directed movements, ataxic features become more clearly recognizable by coordination impairment. These cerebellar ataxic features are characterized by an impairment of smooth, goal directed movements and reduced fine-tuning in speed, force and



**Fig. 1 – Clinical diagnostic algorithm in Early Onset Ataxia (EOA).** This figure displays the diagnostic algorithm for the diagnostic process of Early Onset Ataxia. The consecutive steps of the algorithm will lead the clinician through the diagnostic process. #See Table 2 for oculomotor features in EOAc and Table 3 for the Inventory of non-ataxic signs (INAS); \*See Tables 1 and 4 for paroxysmal ataxic disorders and (tri)nucleotide repeat disorders, respectively. The box “other abnormalities” of the MRI also includes cerebellar hypoplasia and cerebellar atrophy. +See Tables 5 and 6 for the differential diagnosis on cerebellar hypoplasia and cerebellar atrophy on MRI, respectively. %See Table 7 for additional laboratory investigations; \*See Supplementary Table II – IV for hindbrain malformation panels; @ For NGS we advise to perform Whole Exome Sequencing (WES) first with a specific gene panel (see Supplementary Table I for the whole EOA NGS gene filter), in case this is negative the WES can be opened to review all genes. %In case of specific clues pointing to a mitochondrial disorder consider mitochondrial DNA analysis. &In case of no diagnosis consider re-evaluation after >1 year. INAS = Inventory of Non-Ataxic signs; MRI = Magnetic Resonance Imaging; NGS = Next Generation Sequencing; EOAc = Early Onset Cerebellar Ataxia.

direction. There is often a delay in motor milestones, and sometimes also in cognition and speech.<sup>6,14,17,18</sup>

In general, genetic causes of ataxia are associated with an insidious disease onset, whereas acquired ataxias are associated with a (sub-) acute disease onset. There are, however, exceptions to these patterns, as demonstrated by the genetically inheritable disorders causing paroxysmal episodic ataxia with an acute on- and offset. A clinical video-recording of the paroxysmal event may be indicative. When suspected, one should always look for potential triggers, such as physical and emotional stress. These episodic EOAc phenotypes may prompt genetic testing with a specific “NGS panel” for paroxysmal disorders (see Table 1).

Specific cerebellar domains are associated with corresponding features of cerebellar dysfunction including: 1. the vermis and anterior lobe with ataxic posture and gait, characterized by staggering, swaying and titubation, 2. the cerebellar hemispheres with ataxic kinetic limb movements, characterized by intention and action tremor, dysdiadochokinesis, dysmetria, dysarthria and dysrhythmia of speech, and 3. the vermis and flocculus with oculomotor dysfunction, including saccadic eye movements, disorders of smooth pursuit, fixation instability and ocular alignment disorders, see Table 2.<sup>19</sup> In addition to the cerebellar role in coordinative motor function, the cerebellum also plays a role in cognitive and limbic functioning.<sup>20</sup> Through cerebro-cerebellar pathways, the cerebellum may affect language, working memory, visuo-spatial organization and procedural learning.<sup>21–24</sup> Current data indicate that the cognitive domains of the cerebellum are located in the hemispheric cortex of the posterior lobe, whereas the limbic domains are located in the posterior vermis.<sup>25</sup> Cerebellar tumor surgery of these cognitive and limbic domains can induce the cerebellar mutism syndrome, resulting in neuropsychiatric symptoms, mood disturbances and mutism.<sup>20,26</sup> The underlying pathogenesis is still unknown and there are no identified genetic associations.<sup>20,26</sup>

## 2.2. Exclusion of cerebellar ataxia mimics

After recognition of ataxic features, the first step is to exclude cerebellar ataxia mimics, such as sensory ataxia. Damage to

the peripheral nerves, spinal ganglia and dorsal columns can disturb the cerebellar input signals, causing sensory ataxia, whereas the cerebellum itself may still be intact. Analogous to cerebellar ataxia, sensory ataxia may cause a broad based gait and dysmetria. Moreover, cerebellar and sensory ataxia can even concur in the same patient (e.g. in patients with Friedreich's ataxia or Ataxia with vitamin E deficiency (AVED)), which may complicate distinction. In such cases, one can recognize a strong sensory component when eye closure causes an instantaneous worsening of movement coordination or when deep tendon reflexes are reduced or absent.

Other potential mimics of cerebellar ataxia are vestibular dysfunction (often associated with hearing impairment, vertigo and gaze-evoked nystagmus), developmental conditions (including physiological age-related movement disorder-like features, developmental coordination disorder (DCD), myopathies, connective tissue disorders and hypotonia with hypoactive muscle activation (HHM)).<sup>27–33</sup> Finally, EOAc should be distinguished from action myoclonus and dystonic tremor, which may sometimes mimic the features of an ataxic intention tremor.

### 2.2.1. Developmental coordination disorder (DCD)

In children with Developmental Coordination Disorder (DCD), coordination impairment by clumsiness should be distinguished from the presence of an ataxic movement disorder. According to the DSM-V criteria, DCD is characterized as a developmental disorder, not attributable to physiologic immaturity, resulting in non-progressive motor incoordination, interfering with daily activities or academic achievements, after exclusion of neurological, visual and/or intellectual disorders.<sup>34</sup> Although children with DCD might also reveal mild, non-progressive ataxic features, careful longitudinal assessment of the above mentioned DCD criteria could help to differentiate between EOAc and DCD. Longitudinal assessment of DCD criteria should include a broad functional evaluation of the participation in daily activities, communication, cognitive and behavioral functioning. Furthermore, the presence of specific oculomotor symptoms and/or other, (non-)neurologic symptoms may help to distinguish EOAc from DCD patients (see Tables 2 and 3).

**Table 1 – Genes causing paroxysmal ataxic disorders in children.**

Gene (OMIM)	Disease name	Inheritance	Additional features
KCNA1 (176260)	Episodic Ataxia type 1; (EA1)	AD	Between attacks myokymia and epilepsy
CACNA1A (601011)	Episodic Ataxia type 2; (EA2)	AD	Between attacks nystagmus and gait ataxia
1q42 (606554)	Episodic Ataxia type 3; (EA3)	AD	#
CACNB4 (601949)	Episodic Ataxia type 5; (EA5)	AD	Between attacks down beat and gaze-evoked nystagmus
SLC1A3 (600111)	Episodic Ataxia type 6; (EA6)	AD	Between attacks horizontal gaze-evoked nystagmus
PRRT2 (614386)	Paroxysmal Kinesogenic Dyskinesia (PKD)	AD	Dystonia and/or chorea during an attack
SLC2A1 (138140)	Glucose Transporter deficiency (GLUT-1)	AD	In children associated with epilepsy and encephalopathy
ATP1A3 (182350)	CAPOS (Cerebellar ataxia, Areflexia, Pes Cavus, Optic atrophy and Sensineuronal deafness)	AD	Areflexia, pes cavus, optic atrophy and sensineuronal deafness. Can start as episodic ataxia, provoked by fever. The disease course is mostly progressive

OMIM = Online Mendelian Inheritance in Man; AD = Autosomal dominant; AR = Autosomal recessive. # episodic ataxia type 3 is not associated with a specific gene mutation, but with a known locus on chromosome 1q42.

**Table 2 – Cerebellar oculomotor features.**

Cerebellar oculomotor features	Description of the oculomotor feature	Diseases in which these features could be present
<b>Saccadic eye movements</b>		
Saccadic dysmetria	Either hypometria or hypermetria	AT; FRDA; AOA1; AOA2; Tay Sachs; EA2; SCA1; SCA2; SCA3; SCA17; SCA28
Saccade initiation delay (ocular motor apraxia)	Delayed initiation of saccades. Patients use their head (or they blink) to rapidly shift their direction of gaze	AOA1; AOA2; AT; Joubert syndrome
<b>Smooth pursuit of eye movements</b>		
Slow smooth ocular pursuit	Jerky tracking of a visual target (visual as saccades)	FRDA; SCA1; SCA2
<b>Signs of fixation instability</b>		
Gaze-evoked nystagmus	Ocular oscillations observed while the eyes are off center. Gaze-evoked nystagmus can either be horizontal or vertical. The fast phase is in the direction of the gaze.	FRDA; AOA1; AOA2; AT; EA2; SCA1; SCA2; SCA3; SCA5; SCA6; SCA17
Rebound nystagmus	Transient nystagmus observed when the eyes are midcenter. The fast phase beats to the opposite side of the initial direction of gaze	FRDA; SCA1; SCA3; SCA6
Downbeat nystagmus	During midposition, nystagmus occurs with the fast phase downwards. The nystagmus is exacerbated during downgaze and lateral gaze.	AT; EA2; SCA6; SCA5; SCA17
Upbeat nystagmus	During midposition, nystagmus occurs with the fast phase upwards. The nystagmus is exacerbated during upgaze.	
Periodic alternating nystagmus	Horizontal nystagmus when the eyes are in midposition. The fast phase changes direction gradually after a silent period	FRDA; AT; SCA6
Ocular flutter	Involuntary conjugate, unpredictable horizontal back-to-back saccades during attempted fixation	FRDA
Opsoclonus	Involuntary conjugated multi-directional back-to-back saccades observed when the patient tries to fixate	OMA syndrome
Square wave jerks/microsaccadic oscillations	Intrusive, unwanted involuntary and conjugated saccades which takes the eyes off fixation	Healthy children <sup>a</sup> ; FRDA; AOA1; AOA2; AT; EA2; SCA1; SCA2; SCA3; SCA6
Ocular bobbing	Fast downward movement followed by a slow backward movement to the primary position	
<b>Ophthalmoparesis</b>		
Ophthalmoparesis	Variant degree of paresis of oculomotor muscles	Mitochondrial disorders

Oculomotor features observed in cerebellar diseases, subdivided according to four subcategories. All features are described and diseases in which these features could be present are given in this table. AT = Ataxia Telangiectasia; FRDA = Friedreich's ataxia; AOA = Ataxia with Oculomotor Apraxia; EA = Episodic ataxia; SCA = Spinocerebellar Ataxia; OMA = Opsoclonus-Myoclonus-Ataxia syndrome.

<sup>a</sup> Square wave jerks are also physiologically present in up to 90% of children (until 19 years of age).<sup>19,97</sup>

**Table 3 – Inventory of non-ataxia signs (INAS).**

Non-ataxia signs	Diseases in which this symptom is present
Hyperreflexia	SCA and SCAR
Areflexia	FRDA; AVED; AT; Abetalipoproteinemia; AOA 1–4; CAPOS
Extensor plantar response	FRDA; AVED; Abetalipoproteinemia; AOA type 1-4
Spasticity	SCA and SCAR
Paresis	FRDA, SYNE1, Marinesco-Sjögren syndrome
Muscle atrophy	Marinesco-Sjögren syndrome, AOA1, SYNE1, ARSACS
Fasciculations	SCAR type 8
Myoclonus	SCA type 13 and 14
Rigidity	AOA type 1 and 2, POLG, other mitochondrial diseases, OMA
Chorea/Dyskinesia	Different types of NBIA; Wilson disease; SCA type 2
Dystonia	Different types of NBIA; Wilson disease; AT; SCA type 17, POLG, AOA2, Different types of NBIA; Wilson disease; AOA type 1 and 2; AT; SCA type 2; SYNE1
Resting tremor	AT; NBIA; Wilson disease
Sensory symptoms	Several ataxic disorders are associated with a (poly)neuropathy
Downward gaze palsy <sup>a</sup>	Niemann Pick type C
Oculomotor apraxia <sup>a</sup>	AOA type 1–4; AT; Joubert syndrome
Xanthomas <sup>a</sup>	CTX
Cataract <sup>a</sup>	CTX; mitochondrial diseases; Marinesco-Sjögren syndrome
Optic atrophy <sup>a</sup>	FRDA; CAPOS; KIF1A
Myokymia <sup>a</sup>	EA1
Telangiectasias <sup>a</sup>	AT
Deafness <sup>a</sup>	Peroxisomal disorders; mitochondrial diseases; CAPOS; FRDA
Bilateral alopecia <sup>a</sup>	Gomez-Lopez-Hernandez syndrome

Summary of non-ataxic comorbidity; Table adapted from the Inventory of non-ataxia signs for pediatric EOA,<sup>35,36</sup> which clinicians should look for during neurological examination.

<sup>a</sup> These items are not involved in the INAS, but may provide important clues. ARSACS = Autosomal recessive spastic ataxia of Charlevoix-Saguenay; AVED = Ataxia with Vitamin E Deficiency; AOA = Ataxia with Oculomotor Apraxia; CAPOS = Cerebellar ataxia, Areflexia, Pes Cavus, Optic atrophy and Sensineuronal deafness; GOSR2 = North Sea Progressive Myoclonus Epilepsy syndrome; FRDA = Friedreich's ataxia; KIF1A = Spastic paraplegia type 30; EA1 = Episodic ataxia type 1; SCAR = Spinocerebellar Ataxia Autosomal Recessive; SCA = Spinocerebellar Ataxia; SYNE = Spinocerebellar ataxia autosomal recessive type 8; OMA; Opsoclonus-myoclonus-ataxia syndrome; NBIA = Neurodegeneration with Brain Iron Accumulation; AT = Ataxia Telangiectasia; CTX = Cerebrotendinous xanthomatosis.

### 2.3. Exclusion of acquired ataxia

All acquired causes of ataxia (including intoxications, medication side effects, vascular, inflammatory, infectious and deficiencies) should be distinguished from genetic and/or metabolic causes underlying EOAc, see [Supplementary data I](#). This can be performed by a careful evaluation of the disease history ((sub-)acute presentation), MRI and laboratory investigations.

## 3. Step 2: evaluation of non-ataxic symptoms (INAS) and quantification of ataxia symptoms (SARA)

### 3.1. Inventory of comorbid non-ataxic signs

The EOAc phenotype is often complex,<sup>5,6</sup> involving multiple neurologic and non-neurologic signs and symptoms. Comorbid non-ataxic signs can be systematically assessed by the Inventory of Non- Ataxic Signs (INAS), see [Table 3](#).<sup>35,36</sup>

### 3.2. Quantification of the ataxia severity

When the presence of EOAc is established, the severity of the ataxic features can be evaluated by clinical rating scales,

including the International Cooperative Ataxia Rating Scale (ICARS),<sup>37</sup> the Scale for Assessment and Rating of Ataxia (SARA)<sup>38</sup> and the Brief Ataxia Rating Scale (BARS).<sup>39</sup> A brief description of pediatric ataxia rating scales is provided in [Supplementary data II](#). In children older than eight years of age, we have shown that these ataxia rating scales can be reliably assessed (Inter-observer reliability; Intraclass Correlation Coefficient (ICC) 0.91 – 0.99).<sup>40</sup> Due to its brevity, high reliability and frequent application in adult patients, the SARA is often preferred.<sup>41</sup> The CACG-EPNS has recently validated the SARA for age, allowing an accurate longitudinal interpretation of scores against the physiologic age-related values in healthy young children.<sup>29,41</sup> For the quantitative assessment of pediatric EOAc disease progression, standardized SARA video-recordings may be useful. It is important to realize that eye movements should be additionally addressed, as oculomotor function is not included in the SARA, see [Fig. 1](#) and [Table 2](#).<sup>17</sup>

## 4. Step 3: family history and distinct phenotypes

A positive family history with an identified gene defect may prompt direct sequencing of the associated gene. Other information, such as ethnicity and region-specific morbidity

may increase the statistical likelihood of a specific gene defect. Trinucleotide repeat expansions, either inherited or occurring *de novo*, are associated with dominantly inherited spinocerebellar ataxias in children (see also Table 4). Trinucleotide repeat expansions can reveal anticipation, implicating the occurrence of an earlier and more severe disease presentation in successive generations. The appearance of specific features such as downward gaze palsy, telangiectasia and xanthomas may prompt direct testing of the associated gene (see Table 3).

#### 4.1. Friedreich's ataxia

Friedreich's ataxia is one of the most common causes of EOAC, presenting with a distinct phenotype. Friedreich's ataxia is an autosomal recessively inheritable disease caused by a bi-allelic pathogenic variant in *FXN* encoding the frataxin protein. Most patients are diagnosed with an abnormally expanded GAA tri-nucleotide repeat on both alleles, although compound heterozygous mutations involving a pathogenic GAA repeat expansion on one allele and an intragenic inactivating pathogenic variant on the other allele may also be present.<sup>42–44</sup> The clinical presentation is associated with ataxic cerebellar dysfunction, and additionally with loss of deep tendon reflexes, pyramidal tract signs, proprioception, vibration sense, sensory neuronopathy, hypertrophic cardiomyopathy, myopathy, scoliosis, optic neuropathy, diabetes mellitus and hearing disturbances.<sup>42,43,45,46</sup> Oculomotor testing may reveal fixation instability with square wave jerks (Table 2), both during rest and smooth pursuit.<sup>42</sup> If the clinical phenotype resembles that of Friedreich's Ataxia, one should directly test for it, as NGS techniques will not detect repeat disorders.

## 5. Step 4: brain MRI

In absence of a positive clue, the next step is to perform a brain MRI.<sup>47–50</sup> The recommended MRI protocol comprises T<sub>1</sub>- and T<sub>2</sub>-weighted images, Fluid-Attenuated Inversion Recovery (FLAIR), Diffusion Weighted Images (DWI) and Susceptibility Weighted Images (SWI) (to exclude hemorrhage or traumatic brain injury), and consideration of subsequent gadolinium administration and reconstruction in multiple planes

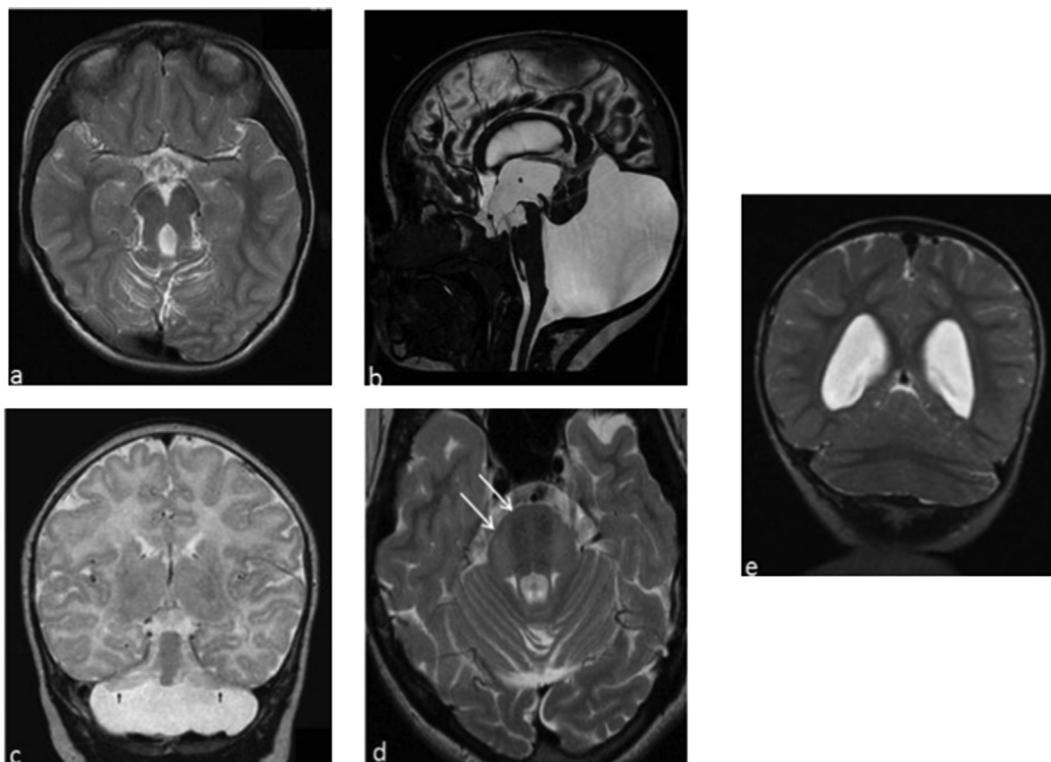
(coronal, sagittal and axial).<sup>47–50</sup> Gadolinium administration can be considered for the exclusion of acquired causes. In case of a congenital disease presentation, gadolinium administration should be restricted, as multiple dosages could lead to depositions in the globus pallidus, dentate nucleus, substantia nigra and red nucleus.<sup>51</sup> On midsagittal T<sub>1</sub>- and T<sub>2</sub>-weighted images, the sizes of the posterior fossa, vermis, fourth ventricle, supra-vermian cistern and brainstem volumes can be easily evaluated.<sup>49,50</sup> In the presence of cerebellar hypoplasia and cerebellar atrophy, secondary enlargement of the fourth ventricle and the supra-vermian cistern may evolve.<sup>49,50</sup> In coronal planes, volumes of cerebellar vermis and hemispheres can be compared.<sup>50</sup> The size, morphology and signal intensity of the cerebellar vermis, cortex, cerebellar white matter and dentate nucleus can be determined on axial T<sub>1</sub>- and T<sub>2</sub>-weighted images. Abnormalities of the cerebellar white matter and cortex are best assessed on T<sub>2</sub>-weighted images.<sup>50</sup>

Three relevant MRI patterns of hindbrain abnormalities are Joubert syndrome, Dandy Walker malformation and pontocerebellar hypoplasia.<sup>52</sup> In Joubert syndrome, the molar tooth sign is considered as pathognomonic. This sign is identifiable on axial planes, consisting of a deep inter-peduncular fossa and elongated, horizontally placed superior cerebellar peduncles (Fig. 2a).<sup>52</sup> In patients with a Dandy Walker malformation there is hypoplasia and anti-clockwise upward rotation of the cerebellar vermis with cystic dilatation of the fourth ventricle, upward displacement of the tentorium (Fig. 2b) and the presence of the “tail sign”, a linear hypointensity in T<sub>2</sub>-weighted images at the inferior portion of the vermis showing a radiological appearance of a ‘tail’.<sup>52–54</sup> Pontocerebellar hypoplasia is characterized by cerebellar hypoplasia (mainly of the cerebellar hemispheres with relative preservation of the vermis) and hypoplasia of pontine structures. In the coronal plane these features can be characterized by a “dragonfly sign” (Fig. 2c).<sup>52</sup> All three patterns of hindbrain malformations may vary in severity and may also include other infra- and supra-tentorial abnormalities.<sup>52,53</sup> If specific features corresponding with one of the three patterns of hindbrain malformations are present, it is advisory to perform direct genetic testing using a specific NGS hindbrain malformation subpanel, see Supplementary Tables II – IV. On MRI, medial T<sub>2</sub>-hypointense stripes and bilateral T<sub>2</sub>-hyperintense signals of the lateral pons merging into a (thickened) middle

**Table 4 – Genetic ataxias caused by a (tri)nucleotide repeat disorder.**

Gene (OMIM)	Repeat	Disease name	Inheritance	Additional features
<i>FXN</i> (606829)	GAA	Friedreich's ataxia	AR	Peripheral neuro (no)pathy, cardiomyopathy, scoliosis, pes cavus
<i>ATXN2</i> (601517)	CAG	Spinocerebellar ataxia type 2	AD	Parkinsonism, myoclonus
<i>CACNA1A</i> (601011)	CAG	Spinocerebellar ataxia type 6	AD	
<i>ATXN7</i> (607640)	CAG	Spinocerebellar ataxia type 7	AD	Retinal changes
<i>ATXN8</i> (613289)	CTG	Spinocerebellar ataxia type 8	AD	Pyramidal signs
<i>ATXN10</i> (611150)	ATTCT	Spinocerebellar ataxia type 10	AD	Epilepsy, pyramidal signs and cognitive problems
<i>PPP2R2B</i> (604325)	CAG	Spinocerebellar ataxia type 12	CAG	Epilepsy, dementia and parkinsonism
<i>TBP</i> (600075)	CAG/CAA	Spinocerebellar ataxia type 17	AD	Psychiatric features and chorea (Huntington like)
<i>HTT</i> (613004)	CAG	Huntington	AD	Psychiatric features, chorea and parkinsonism

Trinucleotide repeat disorders and corresponding genes. Inheritance and additional features are given in this table. OMIM = Online Mendelian Inheritance in Man; AR = Autosomal recessive; AD = Autosomal dominant.



**Fig. 2** – Examples of specific hindbrain malformations on MRI. a) T<sub>2</sub> weighted axial plane showing the typical “Molar tooth sign” of a patient with Joubert syndrome. The figure illustrates the deep inter-peduncular fossa of the mesencephalon. Together with the elongated and horizontally placed superior cerebellar peduncles gives the appearance of a “molar tooth”. b) T<sub>2</sub> midsagittal plane of a patient with Dandy Walker Malformation, showing enlargement of the posterior fossa with an upward displacement of a hypoplastic cerebellar vermis. There is also a cystic dilatation of the fourth ventricle with upward displacement of the tentorium cerebelli. c) T<sub>2</sub> coronal plane showing distinct hypoplasia of both cerebellar hemispheres (as indicated by the arrows) with relative preservation of the cerebellar vermis, often referred to as a “dragonfly” appearance in patients with pontocerebellar hypoplasia, as seen in this patient with PCH type 2. Hypoplasia of the pontine structures can be evaluated on a midsagittal T<sub>2</sub>-weighted image (not shown). d) T<sub>2</sub> axial plane of the pons in a patient with ARSACS (SACS gene) showing distinct medial hypointense pontine stripes (medial arrow). Laterally there is a hyperintense signal of the pons merging into a (thickened) middle cerebellar peduncle (lateral arrow). e) T<sub>2</sub> coronal plane of the posterior part of the cerebellum. There is a clear fusion of both cerebellar hemispheres with the absence of the vermis, indicative of a rhombencephalosynapsis.

cerebellar peduncle may provide a unique diagnostic biomarker for the Charlevoix-Saguenay (ARSACS) syndrome, prompting direct genetic testing for mutations in the SACS gene (Fig. 2d).<sup>55–57</sup> Another distinctly recognizable MRI pattern is rhombencephalosynapsis (Fig. 2e). Rhombencephalosynapsis is characterized by the absence of the vermis and fusion of the cerebellar hemispheres. This can be evaluated on T<sub>2</sub>-weighted coronal images in the most posterior section. Rhombencephalosynapsis is an important key feature of Gómez-López-Hernández syndrome (with other features such as acquired microcephaly, parietal alopecia, trigeminal anesthesia and craniofacial dysmorphic signs). Some patients with rhombencephalosynapsis may also reveal features of VACTERL association. Rhombencephalosynapsis is associated with congenital hydrocephalus due to hypoplasia or a stenosis of the aqueduct. For other recognizable and suggestive MRI patterns in cerebellar disease, see Doherty et al.<sup>58</sup>

In the absence of specific clues, determination of cerebellar hypoplasia or atrophy may help to differentiate between

diagnostic groups. Atrophy can be diagnosed when the cerebellar volume decreases between two successive MRIs. The degree of atrophy depends on the disease stage. This implies that atrophy cannot be diagnosed on basis of a single MRI. However, due to “ceiling effects” at later stages, progression of volume loss may sometimes become hardly detectable during follow-up.<sup>50</sup> The differential diagnosis of cerebellar hypoplasia and atrophy is extensive, involving many genetic and metabolic diseases, see Tables 5 and 6.<sup>49,50</sup> Beside the hypoplasia or atrophy, the radiological differential diagnosis depends on the comorbidity with other MRI abnormalities (such as hypomyelination, other white matter abnormalities, basal ganglia abnormalities etc.), see Table 6. The use of brain MRI is also crucial for the detection of other congenitally acquired cerebellar malformations, such as for instance malformations by cerebellar disruption or hemorrhage. Finally, when abnormalities are consistent with a leukodystrophy, one should consider a specific approach for the determination of “leukodystrophy MRI patterns”.<sup>59</sup>

**Table 5 – Differential diagnosis of cerebellar hypoplasia on MRI.**

Neuroimaging pattern	Disease group	Disease/anomalies
Unilateral cerebellar hypoplasia	Acquired	Second and/or third trimester hemorrhage
	Genetic	PHACE(S) syndrome; Familial porencephaly (COL4A1-mutation)
Cerebellar hypoplasia with mainly vermis involvement	Posterior fossa malformations	Dandy Walker malformation; Joubert syndrome; Rhombencephalosynapsis
	Genetic syndromes	Congenital ocular apraxia type Cogan Acrocallosal syndrome; Gillespie syndrome; Beckwith-Wiedemann syndrome; autism associated chromosome 22q13 terminal deletion.
Global cerebellar hypoplasia	Prenatal infections	Congenital CMV infection
	Prenatal teratogens	Antiepileptic drugs (valproate; phenytoin); retinoic acid; alcohol; cocaine
	Chromosomal abnormalities	Trisomy (13,18 and 21); partial trisomy 12q; monosomy 21q; trisomy 15 mosaicism; monosomy 1p36; ring chromosome 6; <i>de novo</i> X; 8 translocation; 13q12.3-q14.11 deletion
	Metabolic disorders	Adenylosuccinase deficiency; Smith-Lemli-Opitz syndrome; Molybdenum cofactor deficiency and isolated sulfite oxidase deficiency; copper metabolism disease (SLC33A1-mutation); Zellweger syndrome; nonketotic hyperglycinemia; mitochondrial disorders (Leigh disease, pyruvate dehydrogenase deficiency; Mucopolysaccharidoses (type I and II);
Pontocerebellar hypoplasia	Genetic syndromes	Ritscher-Schinzel (3C) syndrome; Hoyeraal-Hreidarsson syndrome; CHARGE syndrome; Endosteal sclerosis; oculocerebrocutaneous (Delleman) syndrome; IER3IP1-mutation; neurofibromatosis type 1; pseudo-TORCH syndrome; velocardiofacial syndrome; oculodentodigital syndrome; Cohen syndrome; Cri du Chat syndrome; Pallister-Killian syndrome; Galloway-Mowat syndrome; Sengers syndrome; OPHN1-related X-linked intellectual disability
	Non-progressive cerebellar ataxias	CAS8; WDR81; ATP8A2; CWF19L1; ITPR1 (SCA15); PMPCA; ATP2B3 (X-linked) and CACNA1A
	Pontocerebellar hypoplasia as defined by Barth	PCH type 1-11
	Cortical malformations	Lissencephaly (RELN, VLDRL, tubulin gens >> LIS1, DCX, ARX); polymicrogyria (tubulin genes, GPR56); periventricular nodular heterotopia (FLNA); primary microcephaly
	Metabolic diseases	Congenital disorders of glycosylation (mostly type 1a but also type 1q)
	Genetic disorders	CASK mutation; Cerebellar agenesis (PTF1A)
	A-dystroglycanopathies	Walker-Warburg syndrome; muscle-eye-brain disease; Fukuyama disease
Posterior fossa malformations	Pontine tegmental cap dysplasia	
Disruptive lesions	Cerebellar agenesis; cerebellar injury secondary to prematurity	

Differential diagnosis based on neuroimaging patterns of cerebellar hypoplasia seen on MRI. Copied and adapted with permission of Wiley and Sons publisher.<sup>49</sup>

## 6. Step 5: laboratory investigations

Laboratory testing can both reveal some of the genetic and acquired ataxias. For laboratory testing of blood, urine and/or cerebrospinal fluid, see Table 7. Disorders that are associated with acquired ataxia are considered at the first step of the algorithm (see also Supplementary data I).

### 6.1. Genetic ataxias associated with biochemical alterations

Ataxia with Vitamin E deficiency (AVED) concerns a rare, autosomal recessively inherited disorder caused by a mutation in the alpha-tocopherol transfer protein (TTPA gene), with a relatively high prevalence in Tunisia and other Mediterranean regions.<sup>60–67</sup> AVED patients may manifest with a heterogeneous phenotype and disease severity, even within families.<sup>65</sup> The pediatric disease onset may range from 4 to 18 years of age.<sup>60,61,64,65</sup> The clinical presentation of AVED

may resemble the phenotype of Friedreich's ataxia with progressive gait and limb ataxia, dysarthria, posterior column involvement, areflexia and extensor plantar responses.<sup>60–67</sup> However, in such cases, comorbid hypertrophic cardiomyopathy may be indicative of Friedreich's ataxia,<sup>64</sup> and comorbid myoclonus, with low serum levels of vitamin E (in presence of normal cholesterol, triglycerides and beta-lipoproteins levels) of AVED.<sup>60–67</sup> Treatment consists of supplementary vitamin E in high doses, which can stabilize and/or ameliorate the neurological deficits. Early therapeutic intervention is associated with a better prognosis.<sup>62–65</sup>

Abetalipoproteinemia is a metabolic disorder caused by an autosomal recessively inherited mutation in the microsomal triglyceride transfer protein (MTTP gene).<sup>68–70</sup> Abetalipoproteinemia is characterized by severe lipid malabsorption from birth onwards. Diarrhea will develop after the first ingestion of milk.<sup>68–70</sup> Due to chronic fat malabsorption, the child fails to thrive and a deficiency of fat-soluble vitamins A, D, E and K

**Table 6 – Differential diagnosis of cerebellar atrophy on MRI.**

Neuroimaging pattern		Diseases
Pure cerebellar atrophy		Ataxia telangiectasia; Ataxia Telangiectasia like disorder; Late-onset GM2 gangliosidosis; Ataxia with oculomotor apraxia type 1–4; PEHO syndrome; CACNA1A-mutation (episodic ataxia type 2; SCA6; familial hemiplegic migraine type 1); mevalonate kinase deficiency; SCAR7 ( <i>TPP1</i> gene); SCAR10 ( <i>ANO10</i> gene); SCAR13 ( <i>GRM1</i> gene); SCAR14 ( <i>SPTBN2</i> gene); SCA29 (point mutations in the <i>ITPR1</i> gene); predominant dystonia with cerebellar atrophy; <i>GRID2</i> mutation; Coenzyme Q10 deficiency; 4H ( <i>POLR3B</i> > <i>POLR3A</i> mutations); <i>CTBP1</i> mutation; mitochondrial disorders
Cerebellar atrophy and hypomyelination		Pelizaeus-Merzbacher disease; Pelizaeus-Merzbacher like disease; Salla disease; 4H; H-ABC; galactosemia; trichothiodystrophy
Cerebellar atrophy and progressive white matter abnormalities	Frontal predominance	Infantile neuroaxonal dystrophy ( <i>PLA2G6</i> mutation)
	Periventricular predominance	Neuronal ceroid lipofuscinoses (particularly late-infantile type); Niemann-Pick type C; Adenylosuccinase deficiency
	Occipital predominance	Early-onset peroxisomal disorders
	Subcortical	L-2-hydroxyglutaric aciduria; Kearns-Sayre syndrome
	Diffuse cerebral	Vanishing white matter disease; mitochondrial disorders
Cerebellar Brainstem	Cerebellar	Peroxisomal disorders; Cerebrotendinous xanthomatosis (CTX)
	Brainstem	Wilson disease; Peroxisomal disorders; Leigh syndrome; dentate-rubral-pallido-luysian atrophy
	Multifocal	Mitochondrial disorders; Galactosemia; Infantile neuroaxonal dystrophy; L-2-hydroxyglutaric aciduria.
Cerebellar atrophy and signal change of the dentate nucleus		L-2-hydroxyglutaric aciduria; CTX; Wilson disease; Succinic semialdehyde dehydrogenase deficiency
Cerebellar atrophy and cerebellar cortex T2-hyperintensity		Infantile neuroaxonal dystrophy; Marinesco-Sjörgen syndrome; congenital disorders of glycosylation 1a; Christianson syndrome; coenzyme Q10 deficiency; late infantile neuronal ceroid lipofuscinoses; pontocerebellar hypoplasia type 7; some forms of non-progressive cerebellar ataxia; some mitochondrial disorders
Cerebellar atrophy and basal ganglia involvement	Calcifications	Kearns-Sayre syndrome; mitochondrial disorders; Cockayne syndrome; Aicardi-Goutières syndrome; MELAS
	Atrophy	H-ABC; Wilson diseases (late); Huntington chorea (inconsistent)
	Signal changes	Mitochondrial disorders; Wilson disease; 3-methylglutaconic aciduria
Differential diagnosis of neuroimaging patterns with cerebellar atrophy. “Atrophy” can only be established after evaluating two successive MRI scans. The Table is subdivided according to MRI findings. Copied and adapted with permission of Wiley & Sons publisher. <sup>50</sup>		

occur. The neurological manifestations of abetalipoproteinemia resemble AVED, since both diseases share vitamin E deficiency as a pathogenic factor.<sup>71</sup> However, in contrast to AVED, abetalipoproteinemia is also associated with low serum levels of cholesterol, triglycerides, apo-B proteins, other fat-soluble vitamins (A, D and K) and acanthocytes in microscopic blood smears.<sup>68,70</sup> Abetalipoproteinemia is treated by a low fat diet and supplementation with fat-soluble vitamins.<sup>68</sup> Vitamin E supplementation may stabilize and/or even improve neurological symptoms.<sup>62–65</sup>

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessively inherited metabolic disorder caused by a mutation in the *CYP27A1* gene.<sup>72–76</sup> CTX is characterized by multi-organ involvement with delayed symptom onset (mean age of presentation is 19 years).<sup>74,76</sup> In children, early disease manifestations may include cataract and intractable diarrhea, followed by tendon xanthomas, neurological symptoms and psychomotor retardation.<sup>74</sup> The neurological presentation of CTX can be subdivided into a classic phenotype with cerebellar signs, parkinsonism and epilepsy; and a spinal phenotype with a chronic myelopathy.<sup>73–75</sup> Other co-occurring neurological features are pyramidal tract signs, dystonia,

palatal myoclonus, cognitive deficits and psychiatric symptoms.<sup>73–75</sup> Biochemically, CTX is characterized by a five- to tenfold increase in cholestanol, normal to low levels of cholesterol and increased urine excretion of urine bile acid alcohol.<sup>77</sup> Neuroimaging plays a significant role in the diagnosis of CTX, demonstrating cerebellar atrophy with white matter changes and increased signal of the dentate nuclei on T<sub>2</sub>-weighted images.<sup>78,79</sup> CTX is treated by the administration of chenodeoxycholic acid which can improve the neurologic symptoms and prognosis.<sup>80,81</sup>

Ataxia with oculomotor apraxia type 1 (AOA1) is an autosomal recessive disorder caused by a mutation in the *APTX* gene, encoding the aprataxin protein. Mean age of disease onset is around 4 years.<sup>82,83</sup> The presenting sign is a slowly progressive ataxic gait. Patients frequently show deficits in initiating horizontal saccades, which defines “oculomotor apraxia”, sometimes compensated by ipsilateral head turning to facilitate saccade initiation. The oculomotor apraxia is present in about 85% of patients with AOA1. AOA1 clinically resembles Friedreich's ataxia, but AOA1 does not include a cardiomyopathy. Additional movement disorders such as dystonia, chorea and myoclonus are much more frequent in

**Table 7 – Additional laboratory investigations.**

Laboratory investigations	Disease groups and specific diseases
<b>Blood investigations</b>	
Leukocytes, thrombocytes, haemoglobin, ammonia, urea, creatine, liver transaminases, blood smear for acanthocytes, biotinidase, thyroid function (TSH, FT4), transferrin electrophoresis, acylcarnitines, lactate, CK,	Metabolic diseases including POLG1
Vitamin B1, B12 <sup>a</sup> and E	AVED, abetalipoproteinemia (Wernicke encephalopathy)
Copper and ceruloplasmin	Wilson disease
Very long chain fatty acids, phytanic and pipecolic acid, bile acids	Peroxisomal diseases
Lysosomal enzymes <sup>a</sup> (ASA, $\beta$ gal, Hex A and B)	Lysosomal storage diseases
Anti NMDA <sup>a</sup>	Auto-immune/paraneoplastic
Albumin	AOA1 and AOA4, CTX
Cholestanol	
Cholesterol, triglycerides	Abetalipoproteinemia, AOA1
Alpha-fetoprotein	AT, AOA2, AOA4 and POLG1
<b>Urine investigations</b>	
Amino acids and organic acids	IEM
Bile acid alcohol	CTX
Urine Homovanillic acid (HVA) and Vanillylmandelic acid (VMA)	OMA (neuroblastoma)
<b>Cerebrospinal fluid investigations</b>	
Glucose <sup>a</sup> , cell count <sup>a</sup> , amino acids, lactate/pyruvate	IEM, GLUT1 and POLG1
Anti-NMDA antibodies <sup>a</sup>	Auto-inflammatory/Paraneoplastic
Laboratory investigations to perform in EOAc. Abbreviations: TSH = Thyroid stimulating hormone; FT4 = Thyroxine; CK = Creatine kinase; ASA = Arylsulfatase A; $\beta$ gal = Beta-galactosidase; HEX-A = Hexosaminidase A; HEX-B = Hexosaminidase B; NMDA = N-Methyl-D-Aspartate; GAD = Glutamic Acid Decarboxylase; POLG1 = Polymerase gamma 1 gene mutation; AVED = Ataxia with Vitamin E deficiency; CTX = Cerebrotendinous xanthomatosis; AOA1 = Ataxia with oculomotor apraxia type 1; AT = Ataxia telangiectasia; AOA2 = Ataxia with oculomotor apraxia type 2; AOA4 = Ataxia with oculomotor apraxia type 4; IEM = Inborn Errors of Metabolism; OMA = opsoclonus-myoclonus-ataxia syndrome; GLUT1 = Glucose transporter 1 deficiency.	
<sup>a</sup> These investigations indicate acquired ataxia and should thus be normal for inclusion in de European Early Onset Ataxia Database.	

AOA1 than in Friedreich's ataxia.<sup>82,83</sup> Moreover, cerebellar atrophy on MRI is more frequently present in AOA1, whereas it is mostly absent in early to mid-stages of Friedreich's ataxia. Supporting biochemical changes include low albumin, and increased blood cholesterol levels. There is no curative treatment for AOA1.<sup>83</sup>

Ataxia with oculomotor apraxia type 2 (AOA2) is caused by bi-allelic mutations in the gene *SETX* encoding senataxin, the second most common recessively inherited ataxic disorder in young adults.<sup>83,84</sup> The AOA2 phenotype resembles AOA1, with respect to a progressive cerebellar ataxia and the co-occurrence of dystonia.<sup>83–87</sup> However in AOA2, the disease onset occurs later (between 11 and 20 years), the neuropathy seems less severe, and oculomotor apraxia is less frequently present (50%) compared to AOA1.<sup>83</sup> Biochemically, AOA2 shows increased alpha-fetoprotein (AFP), but to a lesser extent than in Ataxia Telangiectasia (AT).<sup>82–87</sup> There is no curative treatment for AOA2.

Ataxia telangiectasia (AT) is a rare, recessive, neurodegenerative, DNA repair disorder caused by bi-allelic mutations in the *ATM* gene.<sup>88</sup> Clinically, classic AT is characterized by a cerebellar gait disorder in toddlers, with slow progression over years. Around the age of 5–8 years, oculocutaneous telangiectasia may develop.<sup>88</sup> Associated neurological features include both hypokinetic and hyperkinetic (chorea and dystonia) movement disorders, which may prevail over the ataxia.<sup>89</sup> Peripheral neuropathy commonly develops later in the disease course.<sup>90</sup> Non-neurological signs of AT include immune deficiencies (causing frequent infections) and malignancies (especially lymphoid).<sup>88</sup> Biochemically, AT

is characterized by elevated AFP in serum (in 95% of the patients), which increases during their lifetime, providing a reliable biomarker.<sup>91</sup> Treatment of the neurological signs is symptomatic. However, the systemic manifestations (such as immune deficiency) can be treated with immune-globulins. In AT patients, X-ray examinations should be avoided, due to the propensity of severe radiation induced tissue damage.<sup>88</sup>

## 7. Step 6: Array investigation

In patients with combined features, cognitive impairment, dysmorphism and/or other congenital abnormalities, array CGH (Comparative Genomic Hybridization) may reveal Copy Number Variants (CNV). For chromosomal and/or syndromic diseases presenting with ataxia and/or radiological characteristics of cerebellar hypoplasia/atrophy, see [Tables 5 and 6](#).<sup>49,50</sup>

## 8. Step 7: Next Generation Sequencing (NGS)

Next-generation sequencing (NGS) is the catch-all term for modern sequencing technologies. These include testing of specific gene panels (Targeted Resequencing Panels (TRS)), of coding regions (Whole Exome Sequencing (WES)) with or without a filter for specific genes and of the entire genome (Whole Genome Sequencing (WGS)).<sup>9,10</sup> In recent years, many laboratories apply WES as a diagnostic NGS strategy

for the majority of diagnostic applications. It is important to realize that there are some limitations to these novel techniques. First, one should consider the targeted genes of the panel or filter. Secondly, at this moment NGS does not detect repeat expansion disorders and large rearrangements (deletions and duplications).<sup>9,92</sup> Mutations in noncoding parts of the genome (such as deep intronic regions or promotor regions) can only be detected with WGS. Thirdly, EOAc patients may often present with a mixed phenotype, complicating the selection of the gene panel. Finally, mutations in mitochondrial DNA (mtDNA) might be missed by NGS techniques, requiring separate mtDNA analysis. However, in case of suspicion of a mitochondrial DNA disorder, recent studies advise to start with performing WES analysis first, since this approach has a higher diagnostic yield than with targeted mtDNA analysis (30% of genetic defects were missed with MitoCarta only).<sup>93</sup> For an overview of mitochondrial disorders that are associated with cerebellar ataxia, see [Supplementary Table V](#).<sup>94</sup>

These NGS techniques, including EOA gene panels (see [Supplementary Table I](#)) provide an important step in the algorithm. Firstly, one may perform a WES with a specific EOA gene panel, or another gene panel targeted at co-morbid features. When negative, the WES could be analyzed in total to detect *de novo* mutations as well as presentations of a known Mendelian disease, which has not frequently been associated with EOA.<sup>95</sup> For correct interpretation of the genomic results (including a variant of unknown significance (VUS)), adequate phenotypic assessment and trio analysis of the index patient with both parents is advisory. In absence of abnormalities, trinucleotide repeat expansion disorders and small deep intronic point mutations should be considered. These abnormalities are not detected by current targeted WES NGS techniques. Finally, it is important to realize that the provided gene-list (see [Supplementary Table I](#)), should be continuously up-dated in the future, as newly discovered genes should be added to it, as well.

## 9. EOA database inclusion

As implicated by the enormous variety in underlying genetic and/or metabolic disorders, the EOAc disease spectrum is large. Although application of NGS techniques may result in a higher diagnostic yield, it has been indicated that about 60–70% of EOAc patients may still remain undiagnosed.<sup>96</sup> This is attributable to the potential presence of unrecognized monogenic disorders, complex genetic disorders and disorders caused by epigenetic factors. In this perspective, the CACG-EPNS has collaborated with the adult Ataxia Study Group (ASG) to assemble all EOAc patients in one collaborative international database (<http://arca-registry.org/>) from childhood to adulthood (presently including more than 500 patients, from more than 25 centers worldwide). We hope that a uniform diagnostic algorithm will contribute to 1. novel insights into the longitudinal disease course of underlying disorders; 2. identification of new genes, unraveling complex genetic disorders and the identification of possible epigenetic factors; 3. development of new treatment strategies in larger

homogeneous patient groups; and 4. characterization of transparent markers for monitoring.<sup>6</sup>

## 10. Conclusion

Early Onset Cerebellar Ataxia (EOAc) comprises a large group of rare disorders, with heterogeneous genotypes and phenotypes. In children with early onset cerebellar ataxia, this algorithm may hopefully contribute to the diagnostic process, support the recognition of the underlying diagnoses and provide conditions for optimal usage and interpretation of innovative NGS techniques in EOAc patients.

## Conflicts of interest

None declared.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejpn.2019.08.004>.

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