

Review

Clinical, Cognitive and Behavioural Assessment in Children with Cerebellar Disorder

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Featured Application: The study summarizes the clinical and neuropsychological evaluation in children with cerebellar disorder, highlighting the specific characteristics of the child age useful to define a diagnostic pathway.

Abstract: Cerebellar disorders are characterised clinically by specific signs and symptoms, often associated with neurodevelopmental disorder. While the clinical signs of cerebellar disorders are clearly recognisable in adults and have a precise anatomo-functional correlation, in children the semiotics are less clear and vary with age because of the particular nature of the cerebellum's maturation. Unlike other structures of the central nervous system, this begins at a later stage of foetal development and extends over a longer period of time, even after birth. As a result, the typical signs of cerebellar dysfunction will only become evident when the cerebellar functions have become integrated into the complex circuits of the central nervous system. This means that poor motor coordination in the very early years of life may not necessarily correlate with cerebellar dysfunction, and this may also be encountered in healthy children. The cerebellum's role in cognitive and emotional functions relies on its structure and the complexity of its connections. Cognitive and behavioral impairment in cerebellar disorders can be the results of acquired lesions or the action of genetic and environmental risk factors, to which the cerebellum is particularly vulnerable considering its pattern of development. In the pathological setting, early evidence of cerebellar damage may be very vague, due, partly, to spontaneous compensation phenomena and the vicarious role of the connecting structures (an expression of the brain's plasticity). Careful clinical assessment will nonetheless enable appropriate instrumental procedures to be arranged. It is common knowledge that the contribution of neuroimaging is crucial for diagnosis of cerebellar conditions, and neurophysiological investigations can also have a significant role. The ultimate goal of clinicians is to combine clinical data and instrumental findings to formulate a precise diagnostic hypothesis, and thus request a specific genetic test in order to confirm their findings, wherever possible.

Keywords: ataxia; cerebellar hypoplasia; cerebellar atrophy; developmental delay



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1. Introduction

The cerebellum is part of a complex network of cerebro-cerebellar and cerebellar-cerebral links that connect it to anatomically and functionally distinct parts of the cortex (prefrontal, posterior parietal, superior temporal, and limbic). Its anatomical features and connections clearly reflect its function as an associative area for modulating and harmonising motor, cognitive, and affective behavior [1–3].

To be more specific, the cerebellum is divided into three areas of different phylogenetic origin, each of which is linked through afferent and efferent circuits to structures involved

in processing peripheral information and in the elaboration and execution of motor actions. These areas include:

- The vestibulocerebellum (flocculonodular lobe): this corresponds to the phylogenetically oldest area. The vestibulocerebellum receives information from the visual and vestibular systems, and its output returns to the vestibular nuclei. This cerebellar structure is essential in maintaining balance and coordinating eye movements with movements of the head and body axis. Lesions involving this structure give rise to ataxia and nystagmus (archicerebellar syndrome);
- The spinocerebellum: this includes the cerebellar vermis and the intermediate portion of the hemispheres. It receives sensory and proprioceptive inputs from the spinocerebellar pathways as well as the visual, auditory, and vestibular systems, and it sends messages through the deep cerebellar nuclei to the stations of the trunk and the descending systems (reticular substance, red nucleus, and vestibular nuclei) to the thalamus and the cortex. The structures forming the spinocerebellum have a functional somatotopic representation with a prevalent representation of the trunk and axial musculature in the vermis, and of the musculature of the limbs in the intermediate area. The function of the spinocerebellum is to control and monitor the performance of motor sequences, comparing the spinal marrow inputs and outputs, and modulating the direction and fluidity of the movement. It also has a role in regulating muscle tone by governing the activity of specific motor neurons in the spine. Lesions involving this structure consequently cause ataxia on deambulation, titubation, and limb asynergy, configuring the so-called 'paleocerebellar syndrome';
- The cerebrocerebellum: this constitutes the phylogenetically most recent zone. It is represented by the lateral wall of the cerebellar hemispheres. It receives sensory, motor, premotor, and associative information, not from the periphery, but from vast areas of the cerebral cortex. In turn, it sends output through the dentate nucleus and the contralateral thalamic nuclei in the primary motor cortex and the premotor and prefrontal areas. The lateral cerebellar hemispheres enable movement to be programmed in cooperation with the motor cortex. The cerebrocerebellum has an important role in the temporal regulation of motor sequences (modulating the beginning of the movement and the timing of the alternation between agonists and antagonists, controlling the temporal aspects that affect both perception and action). A lesion at this level within the structure produces clinical signs known as 'neocerebellar syndrome', which is characterised by dysarthria, dysmetria, poor coordination, and impaired cognitive functions [4,5].

2. Clinical Assessment

The clinical picture of cerebellar disease as it appears in adults can't be identified in very early childhood because the cerebellar system is still incomplete at birth.

As a result, even in normal children, cerebellar functions are only acquired during the early years of life and some characteristics of poor motor coordination are physiological in the early stages of development (in the first two years of life). This is why the typical signs of dysfunction (dysmetria and postural instability) only become apparent in a child after the neocerebellar functions have normally integrated at higher system levels.

The clinical signs of cerebellar dysfunctions may appear in various ways, depending on the prevalent site of the lesion and on the child's stage of motor development [6]. In children, there may also be some degree of compensation, depending on the severity of the lesion and the cognitive strategies implemented.

In more detail, in the first year of life, the clinical picture is characterised by: global hypotonia with difficulties in invoking the osteotendinous reflexes; hypotonia that also involves the oral region, with gaping mouth; dribbling; and difficulty in sucking. In some cases, there may be very early signs of nystagmus (both horizontal and rotatory), often associated with ocular dysmetria and slow, irregular oscillatory movements. Already in the first two years of life, there is an evident delay in the acquisition of postural control, albeit

to a variable degree, depending on the severity of the clinical picture and any coexisting cognitive retardation.

In the second year, the clinical signs are more specific and become grossly obvious. At this age, the signs of oral involvement are more readily apparent (chewing difficulties, impaired movements of the tongue and lips, and limited vocal articulation). When the child attempts to remain seated, there is evidence of trunk ataxia, with oscillations in all directions (titubation). There are also early signs of hypermetria during efforts to move closer to objects, with oscillations of the upper limbs and difficulties with fine manipulation due to intentional tremor. The child will have poor temporal coordination in sequences of movements, accelerating, braking, and making abrupt adjustments (synergy). Defensive reactions are also detectable, but they appear to be slow and scarcely effective.

Once the child can stand, the ataxic picture becomes more obvious; the child generally maintains a wider stance, with limbs rotated outwards, and tends to hold onto something to get about. Oscillations of the trunk and head are apparent, whether the child is standing still or attempting to move, and he/she will attempt to correct posture [7]. Children with cerebellar disorders learn to walk unassisted late, generally beyond three years of age, depending on the severity of the condition; in some cases, the child is never able to walk alone.

When the child does succeed in walking, ataxic gait is characterized by a wider base, tilting in all directions, with adjustments and corrections making him/her appear to walk unevenly, in stops and starts, often with arms raised in a defensive gesture. Although the trunk ataxia is a permanent disability, it tends to improve slightly with time because the child adopts compensation strategies [8]. There may also be associated ocular motility disorders, as disruptions in rapid following movements.

From the third year of life onwards, praxis and difficulties in manipulation become increasingly obvious and disabling (impairing the acquisition of personal autonomy), as do the associated the language disorders. In particular, verbal production may be retarded and characterised by dysarthria.

Cerebellum has a key role in the eye movements control. It is involved in the mechanism of image fixation to the fovea to guarantee an optimal vision even when the body and/or the target is in movement [9]. To this aim, different mechanisms are needed, such as saccadic and smooth pursuit control, the vestibulo-ocular and the optokinetic reflex [10]. In cerebellar disorders, the mechanisms underneath eye movements control can be disrupted with the onset of peculiar ocular signs.

Accuracy, velocity trajectory and latency of the saccades can be impaired in cerebellar disorders. Hypermetric saccades are usually observed in cerebellar diseases, while hypometric saccades are mostly seen in brainstem lesions or neurodegenerative diseases [11]. Ocular dysmetria can be disconjugate, with the saccade impairment being bilateral but asymmetric [12].

One possible ocular manifestation of cerebellar involvement is nystagmus, a condition with involuntary rhythmic eye movements that may impair vision.

Nystagmus can be classified in three categories: physiological, infantile and acquired, the three groups presenting differences in amplitude, frequency, direction and other features. In some neurological conditions with cerebellar involvement, nystagmus could appear very early in life and present features hardly discernible from more benign types [13].

A sign of cerebellar or brainstem involvement is fixation nystagmus, which can be observed in primary position and does not disappear but increases during fixation [11].

Gaze evoked nystagmus consists of the impossibility to maintain an eccentric position because of repetitive corrective saccades that reposition the gaze to the primary position. This type of nystagmus is frequent in patients with midline cerebellar lesions [14].

Ocular motor apraxia is been defined as the failure in voluntarily start a horizontal saccade, while vertical ocular movements and smooth ocular pursuit are generally still possible [15,16]. Patients with ocular motor apraxia often try to compensate by turning the head in the target direction [17]; as a result, the head reaches the target before the eyes

do. In 1952, Cogan described this phenomenon in four children and called it “congenital ocular motor apraxia” [18]. Since then, ocular motor apraxia has been described in many other conditions. Most of the children with ocular motor apraxia show other neurological signs, such as hypotonia, ataxia and developmental delay [15,19], which has been kept open the debate between considering congenital ocular motor apraxia as a neurological sign rather than an independent condition [19]. In Joubert syndrome, a congenital brain development disorder which involves the cerebellum and the brainstem, ocular motor apraxia is the most frequent ocular manifestation [17]. Oculomotor apraxia is also a critical sign of a group of autosomal recessive cerebellar ataxias such as ataxia telangiectasia and ataxia oculomotor apraxia type 1 and 2 [20].

It is also well known (confirmed by studies on adult patients with acquired lesions, but also on children with congenital lesions) that the cerebellum plays an important part in the acquisition of certain cognitive and emotional-relational functions, such as planning and visuospatial organisation, language, memory, attention, and affectivity [2,21].

The neocerebellar system (which is of particular interest with regards to the connections with the prefrontal area) is a common site of structural or functional anomalies in neurodevelopmental disorders (autism, evolutonal dyslexia, attention deficit hyperactivity syndrome, metabolic-degenerative diseases, and genetic syndromes) [22].

3. Developmental Cerebellar Cognitive-Affective Syndrome

3.1. *The Role of Cerebellum in Cognition and Emotion: Evidence from Acquired and Congenital Lesions in Children*

Over the last few decades, systematic investigation and substantial evidences have firmly established the role of the cerebellum in higher order functions, such as language, spatial orientation, the ability to organize symbolic functions in sequence, as well as complex emotional and social behaviors [2,3,23]. The relevant question today no longer pertains to whether the cerebellum plays a role in cognition and affect, rather how and through which mechanisms it is accomplished, even in developmental age [23,24].

The first contribute was done by Schmahmann “dysmetria of thought hypothesis”, followed by the conceptualization of the cerebellar cognitive-affective syndrome (CCAS) [1] described in adult patients with focal cerebellar lesions. CCAS is a clinical entity supporting the role of the cerebellum in cognition and affect and has been replicated across disease types and in patients of different ages (for the complete reference list, see [3]).

The substrate of cerebellar role in cognition leads both in its architecture [25] and in the presence of highly organized and functionally specific heterogeneity of its connections with the spinal cord, brainstem and cerebral cortex [3]. Both animal tract tracing and human imaging evidence give insight on the anatomical and functional features of cerebellar connections. The sensorimotor cerebellum mostly in the anterior lobe, adjacent parts of lobule VI, and lobule VIII appears to be an integral part of the distributed neural circuits subserving the motor system (reciprocal connections with motor cortices via the feed-forward motor corticopontine projections and through feed-back to motor regions from cerebellar nuclei via the thalamus); whereas the cognitive cerebellum in the posterior lobe, and the limbic cerebellum (likely represented principally in the vermis), are incorporated into the distributed neural circuits necessary for cognition and emotion (reciprocal feed-forward and feed-back connections with the prefrontal cortex, posterior parietal cortex, superior temporal polymodal regions, cingulate gyrus and posterior parahippocampal area) (for a complete review see [3]).

One primary reason for increased susceptibility of the cerebellum is its protracted developmental timeline compared with the neocortex, which expand the window of vulnerability to a spectrum of neurological and developmental insults, such as genetic mutations, toxic and vascular lesions [2,26]. The cerebellum is among the first brain structures to begin cellular differentiation, and one of the last to fully mature. As such, the developing cerebellum is vulnerable to dysfunction due to genetic and epigenetic factors, toxic in utero environment, focal or global neonatal brain injury, or some combination of aforementioned

stressors. This complexity of risk factors acting over the course of development thus results in a broad range of cellular, morphological, and circuit abnormalities [26].

Acquired focal lesions are a formidable study paradigm as they are discrete and can be precisely defined as for localization, facilitating the study of correlation between function and structure.

In this line, since the CCAS definition, several evidences have been collected in children with cerebellar acute infections [27,28], acquired strokes [29] and tumors rejection [30], supporting the cerebellar involvement in all the high cognitive functions. Studies in acquired lesions provides clinical evidence of functional somatotopic organization of the cerebellum, describing cognitive and executive symptoms associated with lesions to the posterolateral cerebellum and impaired regulation of affect particularly evident when the damage to the cerebellum included the vermis [6].

In conjunction with data about acquired lesions, important evidence also derive from the study of neurodevelopmental and neurogenetic disorders with posterior fossa, and particularly cerebellar, involvement.

Cerebellar malformations are reported in about 200 neurogenetic syndromes (fragile X syndrome, Joubert syndrome related disorders, Williams syndrome, Cockayne syndrome, etc.) as well as in several metabolic/degenerative diseases (congenital disorders of glycosylation or CDG syndrome, neuroaxonal dystrophy, ceroidlipofuscinosis, etc.).

Moreover, congenital or precocious cerebellar anomalies (hypoplasia, agenesis, etc.) are frequently reported in several neurodevelopmental disorders [22,31]. Cerebellar anatomical and volumetric abnormalities are consistently found in children with attention deficit and hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) [32]. Moreover, a cerebellar deficit hypothesis of dyslexia has been investigated [33]. Finally, cerebellar insults represent one of the most important origins of disability among preterm children [34]. In the following paragraphs we will revise the neuropsychological phenotype of neurodevelopmental and neurogenetic conditions with cerebellar involvement.

3.2. Posterior Fossa Malformations Syndromes

The incidence of posterior fossa malformations diagnosed during the newborn period is estimated to be 1 out of 5000 live births [35]. Hypoplasia, atrophy, or a global or partial dysplasia, are associated with 333 different genetic syndromes, including several metabolic diseases [24].

Neuropsychiatric disturbances and cognitive-executive dysfunctions have been described in case series and in samples of children with congenital cerebellar malformations, including cerebellar agenesis, dysplasia, and hypoplasia, molar tooth sign [9,36–38].

Congenital cerebellar malformations are associated in particular with neuropsychological deficits and/or neurodevelopmental disorders, intellectual disability, severe language impairments, and emotional-behavioral problems of varying entities to autistic-like pictures [36]. The type and extent of cerebral reorganization processes in the presence of cerebellar malformations are difficult to predict and may possibly account for the variability of clinical phenotypes. Therefore, it is more difficult to identify a defined syndromic picture just as it is the case with acquired cerebellar lesions [39]. Moreover, many cerebellar malformations are associated with genetic mutations and/or abnormal neuroembryology, thus potential extracerebellar central nervous system effects make it difficult to draw conclusions about function [40].

The isolated inferior vermian hypoplasia and mega cisterna magna tend to have a positive outcome, while vermian hypoplasia and cerebellar agenesis malformations appear to show a moderate or severe degree of neurodevelopmental delay [41].

The behavioral developmental profile of 27 children and adults with congenital malformations confined to the cerebellum showed a pattern of deficits in agreement with the general CCAS profile [39], confirming that malformations of cerebellar hemispheres were associated with selective neuropsychologic deficits in executive functioning, visuospatial and linguistic abilities, while malformations affecting the vermis produced affective and

social disorders evolving towards autistic-like pictures. Motor impairments were generally less severe and showed a slow and progressive improvement.

Recently, hospital records and neuroimaging of 67 children with cerebellar congenital malformations (isolated vermis hypoplasia, global cerebellar hypoplasia, Dandy-Walker malformation, pontocerebellar hypoplasia, molar tooth malformation, rhombencephalosynapsis, unilateral cerebellar malformation) were systematically reviewed by Pinchevsky and colleagues [37] and associations between specific imaging features and neurodevelopmental outcomes were assessed. 85% of the cohort had global developmental delay. Intellectual disability was present in 61% and autism spectrum disorder in 12 percent. Adjusting for supratentorial malformations and presence of genetic findings, severe developmental delay was associated with global cerebellar and ponto-cerebellar hypoplasia, whereas children with vermis hypoplasia were confirmed to be less likely to have severe delay. A worse neurodevelopmental outcome was associated to the presence of epilepsy, but not to supratentorial abnormalities [37].

Cerebellar and brainstem malformation recognizable on axial brain MRI as the “Molar Tooth Sign” (MTS) characterize Joubert syndrome (JS, MIM PS213300) [42,43]. This appearance results from a combination of abnormalities: cerebellar vermis aplasia/hypoplasia, thick and horizontally-oriented superior cerebellar peduncles, and often, a deep interpeduncular fossa. Clinically, individuals with JS typically present as infants with hypotonia, abnormal eye movements, respiratory control disturbances, and as children or adults, ataxia and/or cognitive impairment [44].

Essentially all individuals with JS experience hypotonia and motor delays during infancy and early childhood, usually evolving to ataxia as they get older. Abnormal eye movements and abnormal respiratory control are also seen in most, but may be subtle. Cognition is impaired in most, although a minority of individuals have Intellectual Quotients (IQ) in the normal range [45,46]. In general, adaptive function correlates with cognitive function [45,46]. However, slowed processing speed is common, so neuropsychological and school evaluations should examine both Full Scale Intelligence Quotient (FSIQ) and the Generalized Ability Index (GAI) or similar measures to help contextualize the individual’s intellectual abilities. Because the GAI relies less on speeded and motor tasks, a more accurate representation of cognitive abilities may be ascertained from this or similar scores than from a traditional measure of FSIQ.

For what concerns the emotional and affective development, in JS population only a few patients have a DSM-oriented psychiatric diagnosis, i.e., oppositional defiant and bipolar disorders but many show emotional and behavioral problems, regardless of the level of cognitive functioning, as confirmed by a recent study on a large cohort of 76 individuals [46]. In the fifty-four JS patients described by Bulgheroni et al. [45] the internalizing problems (emotional reactivity, withdrawal, inattention, poor tolerance to frustration) were prevalent but there were no autistic-like behaviors apart from two complex cases with severe intellectual, sensory and motor disabilities.

These studies must be interpreted with caution due to potential ascertainment biases (for more or less severely affected individuals) and difficulties measuring IQ in the presence of significant motor, communication, and visual impairments [38,45].

Other syndromes characterized by posterior fossa malformations but less studied in the neuropsychological domain are Dandy-Walker syndrome, which involves enlargement of the fourth ventricle, absence or hypoplasia of the cerebellar vermis, and sometimes hypoplasia of the cerebellar hemispheres, and Chiari I malformation, consisting of downward herniation of the cerebellar tonsils. Despite large clinical studies in children are still lacking or revealed variable results, it has been argued the importance of cognitive characterization of these patients [47,48].

3.3. Neurodevelopmental Disorders

As previously mentioned, cerebellum abnormalities are associated to various types of neurodevelopmental disorders, the most studied being ASD, ADHD and for some extent, developmental dyslexia [22,32,49–51].

Autoptic studies of patients with ASD have revealed a marked reduction in density of cerebellar Purkinje cells, particularly in the lateral hemispheres [52] and in the vermis [53]. Moreover, studies have reported altered connectivity between the cerebellum and cortical regions in ASD [54], and correlation between cerebellar gray matter volume and social impairment in ASD [49,55].

The important role of the cerebellum and in particular the postero-lateral portions of the hemispheres, in ASD-related behaviors, has been confirmed by a study combining neuroimaging and neuromodulation in humans and mice. Neuromodulation of the right Crus I in typical humans resulted in altered functional connectivity with the inferior parietal lobule, the same circuit presenting atypical connectivity in ASD children. Atypical structural connectivity in the same connection between Right Crus I–inferior parietal lobule was also evident in the Purkinje neuron of the ASD mouse model. Additionally, chemogenetically mediated inhibition of Right Crus I Purkinje Neuron activity in mice was sufficient to generate ASD-related social, repetitive, and restricted behaviors, while stimulation of Crus I rescued social impairment in the ASD mouse model [56].

Dysfunctions of the cerebellum, particularly of the cerebellar vermis, has been accepted as a potential etiological component of ADHD [32,50]. Earlier structural neuroimaging studies with children and adults with ADHD described reduced cerebellar volumes even after correction for total cerebral volume [57,58]. Similarly to ADHD patients, smaller cerebellar volume and reduced GM have been observed in preterm children with impulsive symptomatology [59].

Additionally, abnormal cerebellar connectivity patterns have been described in ADHD children and adults. In adult patients, the cerebellum exhibits reduced connectivity with the prefrontal cortex [60], while altered resting-state connectivity in the cerebellum have been found in ADHD children [61]. Oldehinkel et al. [62] investigated striatal connectivity in an extensive sample of adolescents with a diagnosis of ADHD as well as in their healthy relatives. Hyperactivity, impulsivity and inattention were related to greater connectivity of the posterior putamen with the cerebellum and occipital cortex.

In particular, dysregulation of prefrontal and cerebellar activity seems to be differently involved in neurofunctional subtypes of ADHD models: the inability to engage the cerebellum as well as prefrontal and parietal cortices during response inhibition tasks was found in adolescents with executive deficits, while patients with emotional and motivational deficits over-engaged the amygdala and ventral striatum during rewarded tasks with no change in prefrontal-cerebellar network [63].

The cerebellar deficit hypothesis of dyslexia posits that dysfunction of the cerebellum is the underlying cause of reading difficulties observed in this common learning disability [33]. According to the cerebellar hypothesis, the research group of Nicolson and Fawcett have argued that abnormal cerebellar function impacts not only articulatory and phonological awareness skills, but also skills outside of language that are associated with the cerebellum and reported to be affected in dyslexia, including balance, automaticity, habituation to eye-blink conditioning, and timing skills [51].

However, neuroscience experiments showed limited support to the cerebellar deficit hypothesis of dyslexia [64,65], suggesting that cerebellar dysfunction is not the sole cause of dyslexia, but in some dyslexics it is part of the distributed network of regions that fail to develop and/or fail to wire together properly [66].

3.4. Prematurity

As stated before, cerebellar anomalies are an important cause of disability in premature children [6]. Damages involving the cerebellum can be either direct destructive (haemorrhage, stroke) or related to reduced development (underdevelopment).

The latter seems to be particularly common and is linked to a particular vulnerability of the cerebellum in premature babies. With respect to this vulnerability, the rapid and complex changes that occur in the cerebellar structure during the fetal development play a central role, in particular between the 20th and the 40th gestational weeks when the process of cerebellar foliation is active to guarantee functional differentiation of the cerebellum, just like the convolutions of the cerebral hemispheres [67].

Up to 19% of premature babies with a gestational age of less than 32 weeks have damage to the cerebellum (see [68] for review) and even higher frequencies are found among babies with very low birth weight (<750 g). In particular, cerebellar haemorrhage represents the most commonly acquired lesion of the posterior fossa in preterm children affecting up to 37% of infants born less than 33 weeks' gestational age [34].

In her seminal studies, Limperopoulos studied the prevalence, the neuropsychological profile and the long-term effects of cerebellar damage in premature children [69,70]. It has been shown that cerebellar lesions in premature infants are followed by a significant growth deficit in the contralateral hemisphere evident both at the time of preterm birth and at the correct term age [69]. A cohort of 38 ex-preterm infants with isolated cerebellar damage evident on neonatal MRI, had MRI follow-up performed at the mean age of 35 $\frac{1}{2}$ months (standard deviation: 13.8 months). Unilateral lesions of the cerebellum are associated with a significant reduction in the volume of gray matter in numerous cortical regions contralateral to the lesion (compared to ipsilateral), i.e., dorsolateral pre-frontal, premotor, sensorimotor, medio-temporal and premotor subcortical regions. On the contrary, in the cases of bilateral lesion, there were no interhemispheric differences in tissue volume for any of the regions considered. These results suggest that the growth deficit of brain regions is the result of the interruption of cerebellum-cortical connectivity in favor of the hypothesis of a single anatomical-functional system.

A subsequent study demonstrated a relationship between the remote regional deficit of brain volumetric growth and domain-specific functional disabilities in 40 ex-preterm children with isolated cerebellar damage undergoing neurodevelopmental evaluation and quantitative MRI at the age of 34 months. The authors found significant associations between early signs of autism and volume of the dorsolateral prefrontal cortex, gross motor performance and cortical volumes of the sensorimotor areas, cognitive and language skills, and volumes of the middle premotor and temporal cortices [70].

A review by Limperopoulos and colleagues [71] analysed 12 papers divided into three categories: studies on children with direct cerebellar damage, both haemorrhage and cerebellar stroke; studies on children with underdevelopment of the cerebellum due to the presence of a malfunction in another area in the cerebral hemispheres (diaschisis); studies on premature patients who are born with an underdeveloped cerebellum in the absence of direct cerebellar or cerebral lesions. The latter category is noteworthy since many children have cerebellar hypoplasia or hypotrophy linked to genetic and toxic factors that can cause prematurity; in these cases, therefore, it is not prematurity that causes the injury but vice-versa.

The direct cerebellar insult, which is most concerning prematurity, may be obviously responsible for motor disorders, but also cognitive, socialization and behavioral disorders, revealing a long-term picture of developmental cognitive-affective cerebellar syndrome [71]. The type of direct insult (haemorrhage) is varied, ranging from cerebellar punctate haemorrhages (very small haemorrhages, even less than four millimetres) up to more severe forms.

Children who have a direct cerebellar insult are forty to one hundred times more likely than the normal population to develop an intellectual disability, with an exception for small punctate lesions [71].

It is notably that also among premature children with cerebellar direct damage the functional topography of the cerebellum described in acquired lesions is confirmed, i.e., damages of the cerebellar hemispheres are related to cognitive deficits (posterolateral part of the cerebellar hemispheres), and that bilateral damage determines a more serious

functional outcome. Moreover, the degree of cognitive, linguistic and socio-behavioral impairment correlates with lower volumes of contralateral premotor, midtemporal and dorsolateral pre-frontal supratentorial cortical area, respectively [70].

Regarding the behavioral aspects, a direct cerebellar insult is often correlated to the appearance of internalizing rather than externalizing symptoms, in particular if it is a cerebellar lesion in the vermian site associated with a hypotrophy of the dorsolateral prefrontal cortex there is a greater probability of appearance of autism or autistic-like pictures [71].

A recent review suggested the presence of combined supratentorial injury as a confounding factor that could have an impact on neurodevelopmental outcome in premature children [68]. The authors selected eight studies on preterm neonates (<32 weeks' GA) diagnosed with cerebellar haemorrhage and assessed with standardized and validated neurodevelopmental testing of infants at a minimum age of 12 months, excluding subjects with combined supratentorial injuries. The Authors reported from 43% to 75% of infants severely delayed in cognition, motor, language, and/or behavioral development, with the highest incidence with vermis involvement and with large bleeds [68].

For what concerns reduced cerebellar development/hypoplasia secondary to brain damage or without evidence of direct isolated cerebellar damage or brain injury, cognitive and behavioral deficits are less evident, while are confirmed below-average intellectual abilities, a greater incidence of behavioral problems and psychological distress [71].

4. Diagnostic Approach

While the signs and symptoms of cerebellar involvement in adults are readily recognised, with a precise anatomo-functional correlation, the semiotics are less clear in children, and vary as a function of age. This is because the particular process of cerebellar maturation (unlike that of the other structures in the central nervous system) begins at a later stage of foetal development and takes longer to complete (after birth) [31]. The typical signs of any dysfunction will consequently only become apparent once the cerebellar functions have become integrated into the complex circuits of the central nervous system. As a result, poor motor coordination in the very early years of life is not necessarily evidence of a dysfunction; it can be seen in healthy children too. In cases where cerebellar damage does exist, the early signs may be very vague. This is partly due to spontaneous compensation phenomena, exploiting the vicarious role of the connecting structures (due to the brain's plasticity).

On careful neurological assessment, clinicians are able to attribute a localising value to any signs and symptoms of cerebellar derangements: problems with balance when standing and an associated nystagmus point to damage to the archicerebellar system; asynergy of the limbs combined with ataxia on deambulation suggests that the paleocerebellar system is involved; and dysarthria with an altered spatio-temporal regulation of movements would indicate a lesion affecting the neocerebellar system.

The objective neurological signs must be integrated with data from the child's medical history. It is important to seek any relevant family history pointing to a potentially genetic condition, to analyse the child's pre- and perinatal background, and to assess how the clinical condition evolves [72], particularly distinguishing between 'static' situations which have likely been derived from malformative conditions and progressive situations characterised by developmental arrest or regression suggestive of degenerative diseases [73,74].

While the patient's family history can be important to identify a disorder of potentially genetic origin, it is equally essential to consider the child's physiological history, especially with regards to any significant pre- or perinatal events, and the age of onset of symptoms. The clinician should check for any changes in the patient's clinical condition, to ascertain whether it is static or progressive, thus the clinical follow-up should also include longitudinal observation and careful monitoring of how the child's development evolves.

The availability of scales with validated gait and posture- biomarkers in children is important for diagnostic evaluation. In children with limited concentration and physical endurance, optimally applicable gait and posture biomarkers are characterized as: non-invasive, quick and easy. Until now, insight in the validity of clinically available gait and posture-biomarkers is incomplete. The Scale for the assessment and rating of ataxia (SARA) is an example described as a reliable, quickly assessable, and non-invasive rating scale for patients with ataxia, but there is a clear need to create a specific assessment scale for infant and toddler with items suitable for early developmental stages [75].

An accurate clinical assessment will enable appropriate further instrumental procedures to be arranged. It is common knowledge that the contribution of neuroimaging is crucial to the diagnosis of cerebellar disorders, and neurophysiological investigations can also have a significant role. Extensive and thorough neuroradiological characterisation with magnetic resonance of the brain is the most useful way to identify which further investigations are needed. MRI not only confirms the clinical suspicion of a cerebellar lesion, but also reveals its distribution, extent, and morphology [74]. Cerebellar lesions may occur alone or as part of a more complex malformation of the posterior cranial fossa, or they may be associated with other supratentorial anomalies. Such situations can be encountered both in static encephalopathies and in neurodegenerative diseases and neurometabolic disorders [76].

As mentioned previously, cerebellar anomalies can affect different regions (part or all of the cerebellar vermis or one or both of the cerebellar hemispheres), or they may involve the whole of the cerebellum. It is important to distinguish between these various forms because each of them specifically characterises a different disorder [77].

On MRI, cerebellar hypoplasia can also be differentiated from atrophic changes, this distinction orients the clinician towards a given general pathological category (congenital or metabolic-degenerative). More precisely, in the various anatomical regions, we may find a picture of hypoplasia (a reduction in the number of adequately-sized cells), dysplasia (due to the absence of a part of the cerebellar structure or a disorder of cerebellar neural migration), or atrophy (caused by progressive cell depletion) [78,79]. These three situations can easily be distinguished if the same subject is examined repeatedly at different times; hypoplasia and dysplasia present a static picture, remaining unchanged, whereas the involutonal process of atrophy progresses, becoming increasingly evident over time. Even if only one neuroradiological examination has been conducted, a careful analysis provides clinicians with important information, enabling them to distinguish between a cerebellum, of small size but normal shape (hypoplasia), and an 'involutated' cerebellum with the typically accentuated arborisation of the vermis lobules in sagittal sections, or an increase in the size of the intra-hemispheric fissures (atrophy) [80,81].

With regard to the cognition and behaviour, a comprehensive age-appropriate assessment should always be implemented at the time of diagnosis and at follow-ups, to update the functional profile in order to detect special needs and define appropriate therapeutic and educative interventions in a developmental perspective. The evaluation should include the investigation of psychomotor and intellectual abilities but also of higher cognitive functions, in particular verbal fluency, procedural learning, visual and auditory sequential memory, executive functions (including planning, processing speed, working memory, set shifting and visual attention) together with affect and behaviour regulation, emotional modulation, social and adaptive skills. It is important to adapt the protocol to the clinical and neurological condition of each patient (Table 1).

Through the evaluation of clinical and neuroradiological data, it is therefore possible to formulate diagnostic hypotheses, distinguishing acquired causes (vascular, inflammatory, infectious) and genetic causes. In the genetic field, it is possible to distinguish malformative forms in which the MRI usually shows hypoplasia or dysplasia: among these, the most common are Joubert syndrome and related syndromes and some syndromes as Fragile X and Williams syndrome and pontocerebellar hypoplasia. Among the degenerative forms, characterized by cerebellar atrophy at brain MRI, we mention Ataxia-telangiectasia,

congenital disorders of glycosylation (CDG), spinocerebellar ataxias (SCA). These last ones have a more typical onset in adulthood, although some forms can start also in pediatric age as SCA6, SCA1 and SCA2, particularly for anticipation mechanism. Therefore these conditions should be investigated in case of familial cases.

If a genetic disease is suspected, it is indicated to proceed with the investigation of the specific genetic mutation or in case of less clear hypothesis by next generation sequencing techniques (NGS) of specific groups of genes or of the whole exome.

Table 1. Diagnostic approach in children with cerebellar disorder.

MEDICAL HISTORY
- Family cases
- Pre and perinatal background
- Age of onset
- Static/Progressive evolution
CLINICAL ASSESSMENT
- Anthropometric parameters
- Dymorphisms
- Neurological and cerebellar signs
- Scale of assessment and rating of ataxia
- Cognitive and behavioural evaluation
BRAIN MRI EVALUATION
- Morphology: hypoplasia/dysplasia/atrophy
- Topography: vermis/emispheres/global
- Associated posterior fossa/supratentorial abnormalities

5. Conclusions

Expanding evidence support the presence of cognitive and behavioral deficit related to both direct and indirect cerebellar damages not only in acquired lesions but also in neurogenetic and neurodevelopmental disorders with cerebellar involvement. All of these behavioral and cognitive disabilities can be described in the framework of the developmental cerebellar cognitive-affective syndrome [23,71], and confirms the existence of a functional topography of the cerebellar structure biologically determined, which translates in cortico-cerebellar connections activated at a very early stage during development.

Clinical signs, together with family and patient history must remain the start point to address the patient to further investigations. To this aim, although the instrumental testings are several and potentially useful based on the clinical data, neuroimaging role remains pivotal in the diagnostic approach. The clinician's task is ultimately to integrate the clinical data with the instrumental findings in order to formulate a precise diagnostic hypothesis and thus request specific genetic tests to confirm the diagnosis, wherever possible.

In conclusion, it should be emphasized that it is impossible to outline a standardised and unequivocal diagnostic approach for cerebellar disorders; each patient requires a tailored approach based on their clinical characteristics and neuroradiological findings (in the cerebellum and elsewhere) and on the availability of any further investigation modalities [82].

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