Cerebellar Agenesis

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Abstract

Cerebellar agenesis is an extremely rare condition in which patients show minute cerebellar tissue, usually corresponding to remnants of the lower cerebellar peduncles, anterior vermal lobules, and flocculi. Clinical presentation of cerebellar agenesis may cover a broad phenotypic spectrum of disabilities including not only motor disorders but also cognitive abilities, language disabilities, and affective disorders. The severity and range of motor, cognitive, and psychiatric impairments appears to be correlated with the earliness, localization, and extent of the agenesis of the cerebellum. Patients with congenital malformations display,

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M. U. Manto et al. (eds.), *Handbook of the Cerebellum and Cerebellar Disorders*,
https://doi.org/10.1007/978-3-030-23810-0_84

for example, a more severe and less specific impairment than patients with acquired cerebellar lesions in adult life. The most severe clinical picture is one of patients with involvement of the phylogenetically most ancient structures (complete or partial cerebellar vermis agenesis) as they display severe pervasive impairments in social and communication skills (autism or autistic-like behavior) and in behavior modulation (self-injury and aggressiveness) and marked delays in language acquisition, especially in language comprehension. On the contrary, when the lesions are confined to phylogenetically more recent structures such as cerebellar hemispheres, the clinical picture is characterized by mild cognitive impairment or borderline IQ, good social functioning, and context adjustment abilities with a more favorable prognosis.

In conclusion, it is possible to argue that cerebellar agenesis, in spite of having an extraordinary neuroradiological picture, is a clinical condition compatible with a productive although limited life, especially if the affected person has the opportunity to undergo a rehabilitation program at an early stage of his life.

Keywords

Cerebellum · Agenesis · Hypoplasia · Development · Posterior fossa · Neuroimaging · Embryological · Genetic · Acquired · Disruption · Vermis · Hemispheres · Motor · Cognitive · Midbrain-hindbrain · Aplasia · Classification · Malformation · Pathogenetic · Dysarthria · Executive · Visuospatial · Language · Non-motor · Functions · Learning · Attention · Memory · Affect · Hypotonia (30)

Introduction

Over the past two decades, in light of neuroimaging technique improvement and the development of specific diagnostic protocols, significant progress has been made in the study of posterior fossa disorders. However, several issues still need to be addressed, for example, the distinction between agenesis, hypoplasia, or atrophy. The confusion present in current international literature led Boltshauser, an important author in this field, to title his review on this topic: "Cerebellum-Small Brain But Large confusion" (Boltshauser 2004).

The term *agenesis* refers to the partial or almost complete lack of cerebellum, while *hypoplasia* is the condition for which cerebellar vermis, hemisphere, or both normally exist but are small in size (Boltshauser 2008). Theoretically, the distinction of *hypoplasia* from *atrophy* is quite easy: the first denoting reduced cerebellar volume without loss of tissue which is instead typical in the latter condition (so-called "shrunk" cerebellum) (Poretti et al. 2008). In clinical practice however, distinction between the two is not so simple, especially when there is no possibility to compare multiple images over time (Boltshauser 2004, 2008). All these conditions probably result from different neuropathological mechanisms, acquired disruption versus genetic, or from a different timing in which pathological events occurred during the pregnancy (see below).

Cerebellar agenesis is an extremely rare condition (see Altman et al. 1992 for classificatory criteria).

A literature review reveals that the wording "complete cerebellar agenesis" is quite inappropriate, as postmortem assessment and neuroimaging showed that the majority of patients had considerable cerebellar tissue (Gardner et al. 2001; Zaferiou et al. 2004). Therefore, the corrected designation should be "near total absence of cerebellum." In cases with "subtotal" cerebellar agenesis, minute cerebellar tissues corresponding to the anterior quadrangular lobes were documented by MRI (Sener and Jinkins 1993; Velioglu et al. 1998), and a considerable amount of "rudimentary cerebellum" were reported by neuroimaging or postmortem examination in the studies of Glickstein (1994) and of Leestma and Torres (2000). Complete (total) cerebellar agenesis has never been documented in living subjects (Boltshauser 2008; Poretti et al. 2009). It has been suggested (Zaferiou et al. 2004; Boltshauser 2008) that the term "cerebellar agenesis" should only be applied to patients with minute cerebellar tissue, usually corresponding to remnants of the lower cerebellar peduncles, anterior vermal lobules, and flocculi. In all these cases, the posterior fossa is of normal or increased size and contains the brain stem, showing marked pontine hypoplasia, and a collection of cerebrospinal fluid which passively fills the space normally occupied by the cerebellum.

The clinical presentation of cerebellar agenesis covers a broad phenotypic spectrum of disabilities regarding motor, cognitive, and affective impairment differently combined and with a wide range of severity.

The aim of the present chapter is twofold: first to review and to summarize recent proposals of the embryology and pathophysiology and classification of cerebellar agenesis for a better comprehension of these conditions and second to summarize clinical cases previously described in literature or personally observed to document the clinical profile of this condition and to speculate on cerebellar functions.

Cerebellar Development, Pathological Mechanisms of Cerebellar Anomalies, and Classifications

Cerebellar Development

The development of the posterior fossa begins shortly after neural tube closure when the primary brain vesicles (prosencephalon, mesencephalon, and rhombencephalon) form along the ^anterior–posterior axis of the developing brain (Altman et al. 1992). Between weeks 3 and 5 of gestation, the neural tube bends at the cranial and cervical flexures, and the rhombencephalon subdivides into eight rhombomeres (Niesen 2002). Afterward, the pontine flexure forms between the metencephalon (the future pons and cerebellum) and the myelencephalon (the future medulla oblongata). The isthmus develops at the junction of the mesencephalon and metencephalon and serves as an organizing center for both the midbrain and the structures of rhombomere 1 (Rh1), which will develop into the pons ventrally and cerebellum dorsally. The cerebellum is derived from the dorsal-most domain of rhombomere

1 alar plate, adjacent to the rhombic lip and dorsal roof plate. Within the cerebellar anlage, distinct progenitors give rise to glutamatergic versus GABAergic neurons and two distinct progenitor zone forms marked by distinct transcription factors, Math1 and Ptf1a. These progenitors migrate radially into the cerebellar anlage and give rise to all GABAergic cerebellar cells, including Purkinje cells, GABAergic deep cerebellar nuclei, and interneurons including Basket and Stellate cells. The lateral flare at the pontine flexure creates the 4th ventricle, the roof of which develops into the cerebellum. Between weeks 6 and 7 of gestation, the flocculonodular lobe (archicerebellum) and dentate nuclei of the cerebellum form. The remainder of the cerebellum develops in a rostro-caudal manner, with the more rostral regions remaining in the midline and develop to form the midline vermis, while more caudal regions move laterally due to forces exerted by the pontine flexure and give rise to the cerebellar hemispheres. The vermis (paleocerebellum) develops and becomes fully foliated by the fourth month of gestation, while the development of the large cerebellar hemispheres (neocerebellum) lags behind that of the vermis by 30–60 days (Altman et al. 1992). Proliferation of the cellular components of the cerebellum continues postnatally, with completion of the foliation pattern by 7 months of life (Loeser et al. 1972) and final migration, proliferation, and arborization of cerebellar neurons by the 20th month of life (Goldowitz and Hamre 1998). The caudal rhombomeres (Rh2–Rh8) develop into the pons and medulla oblongata and form the nuclei of cranial nerves 5–10 (Altman et al. 1992; Cordes 2001). In conclusion, between the 20th and 40th week of gestation and during the first few months of life, the cerebellum undergoes a rapid size increase, unparalleled by that of any other cerebral structure (Limperopoulos et al. 2005; Clouchoux et al. 2012; Leto et al. 2016). Growing evidence supports the crucial role of the cerebellum during early development, a period of intense skill acquisition, for the optimization of both structure and function in the developing cerebral cortex (Limperopoulos et al. 2010; Wang et al. 2014; D'Mello and Stoodley 2015; Moberget et al. 2015; Stoodley and Limperopoulos 2016). Emerging evidence from fetal, neonatal, and pediatric populations supports the existence of a regional functional topography of the cerebellum, providing hypotheses to clarify the role of the cerebellum in motor, cognitive, and social/behavioral development (Limperopoulos et al. 2005; Clouchoux et al. 2012; Stoodley and Limperopoulos 2016). It is well known that the cerebellum provides a modulatory function via cerebro-cerebellar loops with sensorimotor, associative, and limbic regions of the cerebral cortex for higher-level motor, cognitive, and behavioral tasks and is involved in various types of implicit/procedural learning (Timmann et al. 2010), supporting new stages of representation throughout cognitive development (Karmiloff-Smith 1995). In this way, the cerebellum guides the optimization of cerebral cortical circuits throughout childhood and into adolescence (Stoodley and Limperopoulos 2016). Furthermore, it has been suggested that the cerebellum has a crucial role in the structural and functional optimization of the developing brain (Wang et al. 2014; D'Mello and Stoodley 2015; Stoodley and Limperopoulos 2016) and that it is involved in structuring the specialization of cortical regions involved in cognitive processes. This developmental pattern suggests the presence of a critical period during cerebellar development

that is central to both the cerebellum's vulnerability and the developmental repercussions of damage which are capable of disrupting this highly regulated, programmed developmental course. Early cerebellar damage can lead to structural alterations beyond the fetal and neonatal period reflecting the impact of an early cerebellar lesion on neural function. Structural neuroimaging studies highlight the reduction of both cerebro-cerebellar white matter pathways and gray matter volume of distal regions of the cerebral cortex to which the cerebellum projects, supporting the developmental diaschisis model proposed by Wang et al. (2014). Early disruption of the cerebellum (i.e., malformations), cerebellar posterior fossa tumors in early childhood, and neurodevelopmental disorders lead to significant long-lasting and wide-ranging changes in the structure and function of cerebro-cerebellar systems. Due to compensatory plasticity, cerebellar damage that occurs earlier in life can result in wide-ranging developmental (motor, cognitive, linguistic, and behavioral) outcomes (Levisohn et al. 2000; Riva and Giorgi 2000; Scott et al. 2001; Limperopoulos et al. 2007; Tavano et al. 2007a; Kirschen et al. 2008; Davis et al. 2010; Stoodley and Limperopoulos 2016).

Pathological Mechanisms of Cerebellar Anomalies

In recent years, the growing use and the increasing improvement of neuroimaging techniques allowed for the identification and accurate description of developmental anomalies of structures in the posterior fossa and particularly of the cerebellum (Boltshauser 2004, 2008; Poretti and Boltshauser 2015; Poretti et al. 2016). Nevertheless, some difficulties remain for definite and precise categorization of the clinical picture observed depending on whether they are a congenital malformation or are resulting from a disruption (Poretti et al. 2009).

The first results from an intrinsically abnormal developmental process, while the latter results from an extrinsic breakdown of (or an interference with) an originally normal developmental process (Reardon and Donnai 2007). Moreover, the same disruptive agent can cause different neuroradiological patterns, which can likely result in a wide morphological spectrum. A clear classification of these patterns remains difficult to achieve. It is expected that at least part of the present uncertainty will be resolved with progress in the understanding of cerebellar embryology and the pathogenetic mechanisms of the different disruptive agents (Parisi and Dobyns 2003; Barkovich et al. 2009).

Indeed, recognition of cerebellar disruptions and their differentiation from cerebellar malformations is important in terms of diagnosis, prognosis, and genetic counselling (Poretti et al. 2009, 2013, 2016; Poretti and Boltshauser 2015; Bosemani and Poretti 2016).

Pathogenesis of cerebellar development anomalies including partial or total cerebellar agenesis is still under debate. They may be secondary to a large number of pathological events either genetic or acquired and genetic factors that could contribute to disruption susceptibility (Boltshauser 2008; Poretti et al. 2009, 2013, 2016; Poretti and Boltshauser 2015; Bosemani and Poretti 2016). Genetic causes

include chromosomal copy number aberrations such as trisomies 9, 13, and 18; chromosomal rearrangements such as del 1q44, del 22q11.2, dup 9p, del 13q2, del 2q36.1, and del 3q24 (Melaragno et al. 1992; Chen et al. 2005; McCormack et al. 2003; Ballarati et al. 2007; Jalali et al. 2008; Boland et al. 2007; Hill et al. 2007; van Bon et al. 2008); and single gene mutations such as *OPHN1*, *FOXC1*, *CASK*, and *ZIC* (Zanni et al. 2005; Aldinger et al. 2009; Grinberg and Millen 2005; Najm et al. 2008). Sometimes, midbrain and hindbrain malformations (Alkan et al. 2009) and cerebellar malformations are associated with more complex genetically determined brain malformations, such as lissencephaly spectrum due to *RELN* gene (Hong et al. 2000; Ross et al. 2001; Miyata et al. 2004), bilateral frontoparietal polymicrogyria due to mutations of *GPR56* gene (Chang et al. 2003), and tubulinopathy due to mutations in alpha and beta tubulin genes (*TUBA1A*, *TUBB2*, and *TUBB3*) (Oegema et al. 2015; Romaniello et al. 2017). Some types of congenital muscular dystrophies (Barkovich 1998; Philphot et al. 2000), pontocerebellar hypoplasia (Uhl et al. 1998; Barth 2000; Doherty et al. 2013; Aldinger and Doherty 2016), and Poretti-Boltshauser syndrome mutations due to *LAMA1* gene (Micalizzi et al. 2016) have also been described. Mutations in *PTF1A* gene (10p12.3 locus) can be seen (Sellick et al. 2004; Millen and Gleeson 2008; Tutak et al. 2009; Al-Shammari et al. 2011; Houghton et al. 2016; Gabbay et al. 2017) in patients with cerebellar agenesis and diabetes mellitus. This gene expressed in the cerebellar ventricular zone plays a crucial role in cerebellar GABAergic neuronal specification and cerebellar neurogenesis. In the animal model, absence of transcription factors ptf1a causes the failure to generate GABAergic neurons and secondarily leads to massive prenatal death of all cerebellar glutamatergic neurons due to the absence of GABAergic synaptic partners. In a recent study conducted by Millen et al. (2014), ptf1a is considered to be the first gene involved in the segregation of the cerebellum from the more ventral brain stem during development. Among metabolic disorders (Steinlin et al. 1998), the most important are congenital disorders of glycosylation (Kier et al. 1999; Freeze 2001).

As far as acquired causes are concerned, toxic agents such as anticonvulsant drugs (Squier et al. 1990) or cocaine exposure (Bellini et al. 2000), intrauterine death of one fetus in a monochorionic twin pregnancy, and vascular disruption which includes ischemic or hemorrhagic lesions during pregnancy, particularly around 24 weeks of gestation (most vulnerable time), can all lead to multiple brain malformations involving the developing cerebellum (Poretti et al. 2013; Bosemani and Poretti 2016; Poretti et al. 2016). Unilateral cerebellar aplasia may be the result of a unilateral disruptive event, while an early bilateral disruptive event could lead to cerebellar agenesis (Boltshauser 2004). Occasional findings show unilateral cerebellar hypoplasia or aplasia associated with a complex brain malformation such as holoprosencephaly (Poretti et al. 2009) or with syndromic phenotypes (Dhillon et al. 2001; Titomanlio et al. 2006). Cerebellar agenesis is also found in patients affected by prenatal infections, particularly cytomegalovirus (CMV) which has an indirect role in inducing neuronal loss by apoptosis and by activating neuroinflammatory responses. The occurrence of this event around week 24 of gestation interferes with the mechanism of neuronal migration either in cerebral or in cerebellar cortex with

decreased proliferation and differentiation of granular neuron precursors (Barkovich et al. 1994). Indeed, it is conceivable that cerebellar agenesis represents the most severe form of the spectrum of cerebellar disruption (Boltshauser 2008; Poretti et al. 2009, 2013, 2016; Poretti and Boltshauser 2015; Bosemani and Poretti 2016).

Classification Systems

Over the years, classification schemes for malformations of posterior fossa structures have been proposed, but none are comprehensive or widely used (Patel and Barkovich 2002; Parisi and Dobyns 2003; Barkovich et al. 2007, 2009; Cotes et al. 2015). The heterogeneity of malformations and the prolonged period of development of the cerebellum make it difficult to understand the pathogenesis of cerebellar malformations and the correlation between the morphological and ontogenetic subdivisions (Doherty et al. 2013; Poretti et al. 2016).

Parisi and Dobyns (2003) and Barkovich et al.'s (2007, 2009) classification systems used an approach that tried to relate malformations to the embryological structures involved and their development and genetic bases. The aim of these classifications is to expand knowledge regarding neuroembryology, developmental biology, and molecular genetics in a flexible system, allowing to unravel their relationship and to clarify these groups of disorders. Moreover, the flexibility of these classifications should facilitate the description of new embryologic processes and the discovery of novel malformations. Accordingly, Barkovich et al.'s (2009) classification system divides midbrain and hindbrain malformations in four groups: malformations secondary to early anteroposterior and dorsoventral patterning defects; malformations associated with later generalized developmental disorders that significantly affect the brain stem and cerebellum; localized brain malformations that significantly affect the brain stem and cerebellum; and combined hypoplasia and atrophy in putative prenatal onset degenerative disorders. Notably, distribution of malformations within each group can change depending on our knowledge of the malformation, of its cause, or of the processes involved in midbrain-hindbrain development changes.

This classification of cerebellar malformations differs substantially from those previously proposed which were largely based on the anatomic regions involved (Patel and Barkovich 2002). However, despite this considerable effort, it is still more functional to use the classification system based on radiological findings of MRI (Patel and Barkovich 2002) in order to categorize cerebellar malformations through a systematic approach. Cerebellar malformations can be grouped into two broad categories distinguished by the presence of hypoplasia versus dysplasia. Cerebellar hypoplasia (CH) is further subdivided into focal hypoplasia (isolated vermis hypoplasia and hemisphere hypoplasia) and generalized hypoplasia (Dandy-Walker continuum, pontocerebellar hypoplasia). Based on this classification, the spectrum of abnormalities including CH is wide, ranging from mild hypoplasia to severe cerebellar hypoplasia and complete unilateral cerebellar aplasia (UCA) (unilateral absence of a cerebellar hemisphere). Nevertheless, the

hypothesis about the acquired disruptive process underlying UCA should be interpreted with caution, particularly when regarding "one hemisphere hypoplasia" as a cerebellar malformation in the scheme proposed by Patel and Barkovich (2002) (Boltshauser 2004; Bosemani and Poretti 2016). It is important to note that the severity of cerebellar abnormalities usually correlates with the timing of the disruption during the pregnancy.

Cases Report

Literature Review

Clinical pictures of near total absence of the cerebellum described in literature show a wide phenotypic heterogeneity ranging from subjects with severe impairment that does not allow for long-term survival to persons who have reached adulthood or young adulthood with deficits that variously affect motor, cognition, and behavior.

The first group includes subjects with a severe clinical picture, always associated with other brain malformations or with complex syndromes and with death within the first days or weeks of life. There are few reports in literature: the earliest descriptions date back to Verdelli (1874), Leyden (1876), Borrell (1884), and Priestly (1920) who described cases who died in the neonatal period and in whom near total cerebellar agenesis was associated with hydromyelia, syringomyelia, and meningocele. More recently Riccardi and Marcus (1978) described a case with nearly total cerebellar agenesis in the context of a complex syndrome, associated with presumably X-linked hydrocephalus, who died during the third month of life. Hoveyda et al. (1999) reported a case with neonatal diabetes mellitus and microcephaly surviving only up to the first month of life. Descriptions by Leech et al. (1997) and Van Coster et al. (1998) of some cases with similar findings allowed Sellick et al. (2004) to identify the genetic mechanisms underlying this syndrome, mutation in *PTF1A* gene, subsequently confirmed by Millen and Gleeson (2008) and by Tutak et al. (2009).

In the literature, cases of cerebellar agenesis surviving until adulthood are quite rare. The first was described by Combettes (1831), and again by Ferrier (1876), and Fusari (1891). Combettes described a female who died at the age of 11 with severe motor difficulties (she had learned to walk at the age of 5) as well as cognitive and linguistic deficits (she did not speak until she was 3). Analogously Sternberg (1912) described the case of a woman who died at 46, with marked developmental delay (she learned to walk and to speak at the age of 6 and started school and learned to read and write when she was 10 years old). Anton and Zingerle (1914) reported a girl who learned to walk at 4 years old and to speak at the age of 5. A similar pattern of developmental deficits is described in other single cases descriptions by Baker and Graves (1931), Boyd JD (1940), Cohen (1942), and Tennstedt (1965). Specifically, Stewart (1956) thoroughly described the case of a man surviving until the age of 55 whose autopsy showed near complete aplasia of the cerebellum as only a single minute fragment of cerebellar substance was detected. The patient, born in 1883 after

a complicated delivery due to the large size of his head, appeared abnormal since birth. The age at which he started to crawl is unknown, but he learned to walk after the age of 7. All movements were clumsy. He was very slow in buttoning and unbuttoning his clothes and often required assistance. He fell down frequently but was able to climb stairs unaided. Speech was acquired late, and articulation, although gradually improving over the years, never became distinct. Due to his obvious mental retardation, he remained in elementary school until the age of 14 without learning anything. He played with toys and was friendly with other children. In terms of temperament, he was good-natured and easily managed. Throughout his life, he became progressively more responsible even though he never became independent. After the death of his parents, he was moved to an institution. His clinical condition remained stable for a long time and worsened dramatically only in the last year of his life when he lost the ability to walk and move.

Glickstein (1994) reviewed all the literature on these historic cases, particularly focusing on the case already described by Boyd JD (1940). He sought to rebut common thinking, often repeated in textbooks, that people with cerebellar agenesis may develop completely normal movements and never show any sign of movement disorders. At the end of his work, Glickstein (1994) concluded that people born without cerebellum are profoundly impaired in motor development and are slow in walking and talking and they always remain very clumsy. Recently, after accidentally finding new documents in his brother's garage, Boyd JD's son updated the case described by his father (Boyd CA 2009). The new data presented a fuller picture of the patient's history: at a neurological exam, the patient appeared as a simple man with some hearing loss, slow slurred speech, and unsteady gait, fair memory of events concerning himself but with limited general knowledge; no emotional defects were observed; he was clean and able to attend to his person; he was able to get around unassisted. He was also employed as a manual laborer.

The case reported by Timman and her group (Timmann et al. 2003; Richter et al. 2005; Nowak et al. 2007) confirmed this data. The patient is a 59-year-old woman with an almost total cerebellar agenesis, who showed mild abnormalities in oculomotor, speech (slurred), and gait control (ataxia) and cognitive impairment. The patient, born after uneventful pregnancy and delivery, presented a slow motor development walking at 3 years old. She was always described as being clumsy with her hands and had speech delays. Indeed her speech was slow and slurred. The lack of coordination is described as having slightly improved over the years. At the age of 7, she started to attend a regular school but never learnt how to read and write apart from her name. After leaving school, she started to work at her parents' farm. She was able to help by working, and she learnt to ride a bicycle. Following a car accident, she severely injured her right hip and was consequently forced to stop working at the farm and started to work in the electronics department of a workshop for disabled people. This patient learned to connect cables with lamps and to screw plugs without significant impairment. She never got married and lived on her own in one of her brother's apartments. She was able to look after the apartment and her finances herself. Neurological examination revealed mild to moderate cerebellar dysarthria and ataxia of the upper and lower limbs, mild ataxia of stance, and impaired gait. Slight oculomotor disorders

were present. In addition, after a more detailed evaluation, problems in her executive, visuospatial, and language tasks were found.

Among the publications of the last two decades (Sener and Jinkins 1993; Sener 1995; Van Hoof and Wilmink 1996; Velioglu et al. 1998; Leestma and Torres 2000; Gardner et al. 2001; Chedda et al. 2002; Titomanlio et al. 2005; Huissoud et al. 2009; Jacob and Goez 2011; Arrigoni et al. 2015; Meola and Fernandez-Miranda 2015; Yu et al. 2015; Brielmaier 2016; Gelal et al. 2016; Mormina et al. 2016; Ashraf et al. 2016), other cases and one fetus have been described, which, although studied in less detail, confirmed that a nearly total absence of the cerebellum can cause many clinical symptoms even if the features and severity can vary from case to case. Motor disturbances which affect walking, writing, and articulation of speech are the most common, even if the case described by Ashraf et al. (2016) showed only cognitive impairment with no motor impairment. Intellectual disabilities cause learning difficulties and limit autonomy. These patients are often not able to live without assistance. However, it is interesting to note that more and more frequently delayed developmental milestones are reported, with a trend toward improvement over time.

These findings are in line with the emerging concept that the cerebellum plays a crucial role in regulation, learning, and automation of complex motor and cognitive tasks (Schmahmann 1996; Thach 1997). There is in fact growing evidence in literature that supports the role of the cerebellum in non-motor functions such as language, learning, attention coordination, planning, memory, and affect modulation (Leiner et al. 1991; Fiez et al. 1992; Schmahmann 1997; Schmahmann and Sherman 1998; Steinlin et al. 1999; Fabbro 2000; Tavano et al. 2004; Gordon 2007; Beaton and Mariën 2010; Murdoch 2010; Schmahmann 2010; Buckner 2013) as well as a role as center for higher cognitive function. The complex set of symptoms exceeding simple motor deficit was first named "Cerebellar Cognitive-Affective Syndrome" (CCAS) by Schmahmann and Sherman (1998), who described adult patients with acquired cerebellar lesions showing impairment of executive functions, visuospatial disorganization, affect changes, and expressive speech/language deficits (agrammatism, mild anomia, dysprosodia). This data was subsequently confirmed by Levisohn et al. (2000) and Riva and Giorgi (2000) in a pediatric population with acquired cerebellar lesions and from Chedda et al. (2002) and Tavano et al. (2007c) in children with cerebellar malformations.

Moreover, these cases highlight the remarkable redundancy present in the developing human brain that allows for a partial compensation of the absent neocerebellum; it should be remarked however that the impairment in these cases of cerebellar agenesis is much less severe than that seen in acute cerebellar damage in adults. The surprisingly preserved level of motor functioning in cerebellar agenesis reflects the efficiency of extracerebellar motor systems which are all preserved in these cases (Lemon and Edgley 2010). In 2016, Dahlem et al. studied the cerebellar contribution to self-motion perception in patients with cerebellar agenesis (previously described by Chedda et al. 2002 and Schmahmann et al. 2007), showing that the perceptual thresholds were elevated in these kinds of subjects and proving that the cerebellum actually plays an important role in the identification of self-motion

cues, contributing to sensory processing in many realms when the behavioral goal is a discriminative rather than a motor task.

Recent Neuroradiological Studies

Recent studies (Arrigoni et al. 2015; Meola and Fernandez-Miranda 2015; Yu et al. 2015; Mormina et al. 2016) have applied DTI and MRI angiography techniques to document extracerebellar lesions secondary to cerebellar agenesis (named cerebro-cerebellar diaschisis) .

Arrigoni et al. (2015) and Mormina et al. (2016) highlighted an absence of the transverse pontine fibers, explaining that the marked pontine hypoplasia is due to cerebellar agenesis and an aberrant course of the cerebello-thalamic, fronto-cerebellar, and spino-cerebellar tracts. Using MRI angiography, Yu et al. (2015) demonstrated an avascular posterior fossa with bilateral absence of posterior inferior cerebellar artery, anterior inferior cerebellar artery, and superior cerebellar artery. DTI showed the complete lack of the efferent and afferent limbs of the cerebellum. In the patient described by Meola and Fernandez-Miranda (2015), the tractography study revealed that cerebellar peduncles were present but atrophic.

Personal Case

Clinical features showed by the subject RG are in line with data present in literature. This patient, presenting near total cerebellar agenesis, was monitored in our Scientific Institute since the age of 4 and was previously described in research papers (Borgatti et al. 2004; Tavano et al. 2007a, b, c; Arrigoni et al. 2015). At the time of the last evaluation, he is a 48-year-old right-handed male. His family has no history of neurologic or psychiatric diseases. His parents were first-degree cousins. Pregnancy and delivery were uneventful. Weight at birth was 2500 g. Since the first month of life, he displayed a delay in neuromotor development and a marked muscular hypotonia. His whole motor development was significantly delayed (control of head movements, 5 months; sits alone for a short time, 24 months; stands holding on to furniture, 9 years; can walk when led, 10 years; takes a few steps alone, 22 years), but RG showed progressive learning of his motor skills up to independent walking at the age of 22. From a relational level point of view, he was described as a very isolated child until the 4th year of life, with autistic-like behavior: he spent much time on his own, did not actively look for company, and showed an interest for stereotyped and repetitive activities. If cuddled, he did not reject the adult. Additionally, language development was delayed (says two clear words, 24 months; uses 9 clear words, 5 years; uses two-word or longer sentences, 6 years; uses more than 2 personal pronouns, 8 years; learning to read and write, 10 years), but the language delay was less compromised than the motor and relational delay. He was visited for the first time at the age of 4 years and 6 months, and since he was 5, he has been attending a special school in our Institute where he lived during the school year.

Since then, RG has always been monitored by our Institute's rehabilitation centers thus allowing us to retrace his life history in detail and witness his progressive learning of new skills. At the age of 10, he started walking with support; he correctly pronounced all single phonemes of the Italian language, but word articulation was still incorrect. Sentences were simple, short, and context-related but sufficient for communicative exchanges with peers. He had learned to read and write in capital letters with many spelling errors. Teachers reported, above all, the fact that his performances significantly improved if someone helped him plan the task and reinforced him to maintain his attention. Furthermore, RG had to be constantly stimulated as it appeared that, if left to himself, he did not show any initiative. When he was 17, he entered a family residence in our Institute where he still lives today in the framework of a rehabilitation program that focuses on the learning of basic self-sufficiency skills. Today, at the age of 48, RG is completely independent in his personal life, his skills are well consolidated, and he continues to acquire new abilities, performs a simple job (assembles electro-technical parts), knows the value of money, is able to go shopping, and has personal interests (music, films) – every week he buys a magazine to choose his favorite TV programs or to inform parents and friends of programs he knows they like. He is able to program a video recorder. He uses a cellular phone not only to call people but also to send short messages. Recently he learnt to use a fretsaw in order to build a simple but functional shoe rack. He has learned to be completely independent in traveling from a town in northern Italy to another: from the community where he lives (in a valley in Lombardy), he takes a bus to a big city (Bergamo) where he stops for some hours during which he has lunch (choosing from several alternatives: small restaurants, pizza houses, cafés) or shops for himself or for friends he will be visiting. He is described as a very determined person able to achieve his goals, provided that he has enough time to learn. The long time he requires is the main limitation to the effectiveness of his learning. Despite his oculomotor disorders, ataxic gait, and cerebellar signs evidenced by the neurological examination, the patient can walk and perform routine daily activities by himself. At the age of 48, a detailed clinical and neuropsychological evaluation as well as a neuroimaging study on a 3 T scanner with DTI and functional (resting-state fMRI) acquisition was performed (Arrigoni et al. 2015). The neuroimaging study confirmed the complete absence of the cerebellum, with a very small component of cerebellar tissue located posteriorly to the midbrain, close to the lamina quadrigemina. The pons was flattened, and a medial notch was evident along the anterior surface of the brain stem. The posterior fossa was entirely occupied by liquid. No supratentorial abnormality was evident, apart from a mild enlargement of lateral ventricles (Fig. 1a). The DTI analysis showed that the overall structural integrity of the white matter is preserved. Moreover, DTI color maps demonstrated, in the brain stem, the absence of cerebellar transverse fibers in the pons and superior cerebellar peduncles and their decussation in the midbrain and fronto-pontine tracts in the mesial part of cerebral peduncles. A tractographic reconstruction obtained from DTI confirmed that apart from corticospinal tract, no cerebellar pathways are present in the brain stem (Fig. 1b). When reconstructed from resting-state fMRI (Fig. 1c), the patient's auditory, visual, somatosensory, default-mode, and executive-function networks appeared to be normal; on the other hand, the executive-control network which involves the dorso-

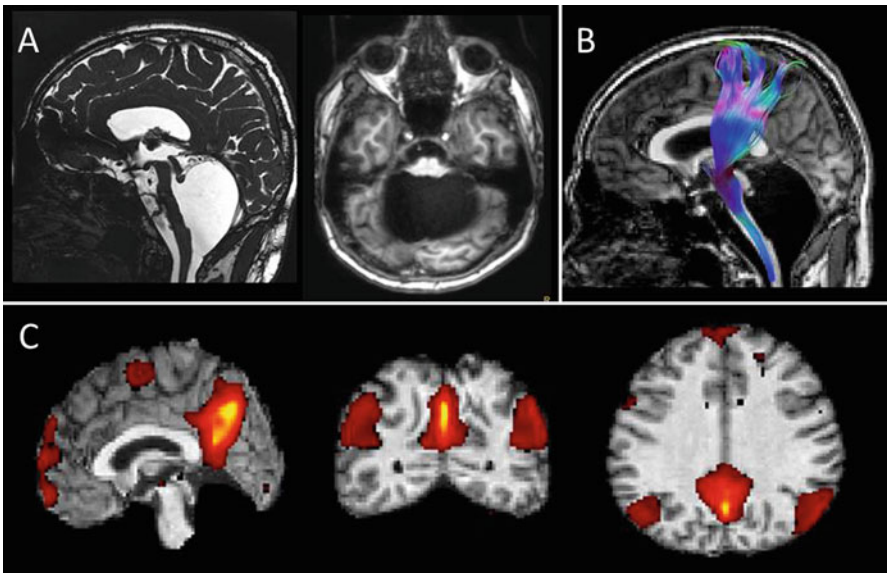

Fig. 1 MRI findings. In panel A, morphological sequences demonstrate the absence of the cerebellum, with an empty posterior fossa and a flattened pons. In panel B, tractographic reconstruction of the corticospinal tract obtained from DTI data is shown. Panel C shows the Default Mode Network (DMN) of the patient, reconstructed from resting-state fMRI

lateral and ventro-lateral prefrontal cortex areas that are strongly connected with the cerebellum via the fronto-pontine fibers was significantly impaired. Neuroimaging results, excluding the involvement of extra-cerebellar structure, support Yu et al.'s hypothesis of a vascular origin of cerebellar agenesis.

The cognitive assessment evidenced a mild impairment with a disharmonic profile (WAIS-R Full Intelligence Quotient (IQ) 69, Verbal-IQ 65, Performance-IQ 82). Performance was more impaired on tasks involving visuomotor integration, motor adaptation and fluency (Coding), working memory (Arithmetic), and extraction of higher-order semantic inferences (Similarities). As for constructional abilities, his impaired performance was mainly due to the extra time he needed to complete the puzzles (Block design). Executive functions such as planning and flexibility as well as focused attention were scarce. On the mirror drawing test (see Arrigoni et al. 2015), the performance was judged according to two parameters that typically characterize the learning process: the decrease in the time needed to solve a task and the increase in accuracy as measured by a decreasing number of errors. The patient's performance slightly improved over time mainly in terms of accuracy, but not in terms of time, and was thus significantly impaired if compared to age-matched normal controls.

With the aim of studying the role of the cerebellum in high hierarchical levels of motor planning, RG underwent a kinematic analysis to compare his performance with age-matched controls in a second-order motor planning task (i.e., the ability to modulate the first act as a function of the nature of the second act). These abilities were successfully learned by RG, despite the expected difficulties in fine-motor

skills (Casartelli et al. 2017). These results suggest intriguing hypotheses on the neural circuits that support distinct stages of the motor planning hierarchy and on the functional role of the second-order motor planning in motor cognition. The cerebellum seems to not be essential for second-order motor planning, but rather, distinct stages of motor planning seem to be supported to varying degrees by different neuronal substrates (i.e., parieto-frontal mirror circuit) preserved in RG.

Furthermore, to understand the causal involvement of the cerebellum in multisensory integration (MSI), RG was tested with a robust psychophysical procedure consisting of measuring the reaction times after the presentation of visual, auditory, and audiovisual stimulus combinations. Although various aspects of perceptual and sensory processing have been linked to the cerebellar activity, the true role of the cerebellum in binding information from different sensory modalities still remains unclear. Experimental results evidenced a marked impairment of MSI in the patient showing the key role of the cerebellum in MSI (Ronconi et al. 2017).

The patient's lifelong ongoing improvement and adaptation raises many questions about the role of the cerebellum in cognition. Conscious and explicit compensatory learning strategies, mainly based on declarative memory and more closely linked to the functions of the cerebral cortex, may have played a role in his development. The cerebral cortex may have progressively compensated for some functions normally controlled by the cerebellum (Ullman 1997). The patient's executive deficits exposed by new neuroimaging and cognitive data demonstrated the impairment of the frontal functions in cerebellum agenesis due to diminished cerebellar connections to these regions. The patient's performance, impaired but showing mild and uneven improvement over time, suggests a putatively increased, although not completely effective, contribution of the basal ganglia to learning tasks, with a persistent impairment in timing, precision, and fluency due to the lacking contribution of the cerebellum. This data is in line with theories on brain plasticity and possible recovery and compensatory mechanisms in acquired or congenital brain lesions (Laforce and Doyon 2002). The patient's overall mild motor and cognitive deficits probably confirm the limitations of cerebro-cortical recovery strategies. The lack of the cerebellum's contribution to timed demands and temporal coordination affected his development, the performance in assessment setting, and, more pertinently, his everyday life. He will never stop learning to compensate for his impairment but will always need a long time to act and consolidate. An enriched environment may have positively influenced the development of the patient: he followed an extended rehabilitation training plan for 15 years, followed by an educational one focused on learning and maintenance of basic self-sufficiency skills. Moreover, the focus on participation and social integration has surely played a significant role in his well-being (Arrigoni et al. 2015).

Clonclusion and Future Directions

From a literature review and our personal experience, it seems evident that cerebellar agenesis brings about a complex behavioral picture which includes not only motor disorders but also cognitive abilities, language disabilities, and affective disorders

(Leiner et al. 1991; Fiez et al. 1992; Schmahmann 1997; Schmahmann and Sherman 1998; Fabbro 2000; Gordon 2007; Beaton and Mariën 2010; Murdoch 2010; Schmahmann 2010). This picture generally overlaps with the symptomatic profile of CCAS (Schmahmann's syndrome; Schmahmann and Sherman 1998). Severity and range of motor, cognitive, and psychiatric impairments appear to be correlated with the time of onset, localization, and extent of the agenesis of the cerebellum (Chedda et al. 2002). Patients with congenital malformations indeed display a more severe and less specific impairment than patients with acquired cerebellar lesions in adult life (Borgatti et al. 2004; Tavano et al. 2007b, c). As reported in a large number of patients, either adults or pediatric displaying either acquired (Levinsohn et al. 2000; Riva and Giorgi 2000) or malformative cerebellar lesions (Chedda et al. 2002; Tavano et al. 2007c), subjects with involvement of the phylogenetically most ancient structures (complete or partial cerebellar vermis agenesis) display the more severe clinical picture. In particular, severe pervasive impairments in social and communication skills (autism or autistic-like behavior) and in behavior modulation (self-injury and aggressiveness) and marked delays in language acquisition, especially in language comprehension, have been described by many authors (Gilbert and Coleman 1992; Schmahmann 1991; Kim et al. 1994; Courchesne et al. 1994; Courchesne 1997; Schmahmann and Sherman 1998; Riva and Giorgi 2000; Fabbro 2000; Mariën et al. 2001; Jansen et al. 2005; Tavano et al. 2007b, c; Tavano and Borgatti 2010; Casartelli et al. 2018). These studies suggested that vermis (in particular postero-inferior lobules) plays a crucial role in processing of complex social and emotional behaviors, a processing that takes place in a complex network involving other associative areas such as the frontal and limbic system.

On the contrary, when the lesions are confined to phylogenetically more recent structures such as cerebellar hemispheres, the clinical picture is characterized by mild cognitive impairment or borderline IQ, good social functioning, and context adjustment abilities (Chedda et al. 2002; Tavano et al. 2007c; Tavano and Borgatti 2010) with a more favorable prognosis.

As previously underlined, cerebellar agenesis represents the most severe form of the spectrum of cerebellar disruption (Boltshauser 2008; Poretti et al. 2009).The more accurate terminology should be "near total absence of the cerebellum" (Gardner et al. 2001; Zaferiou et al. 2004). In fact, a certain amount of "rudimentary cerebellum" is always present in living subjects (Boltshauser 2008; Poretti et al. 2009), usually corresponding to remnants of the lower cerebellar peduncles, anterior vermal lobules, and floccule. Therefore, neuropsychological functioning in these cases is quite similar with that observed in subjects who underwent cerebellar hemispheres lesions, showing favorable evolution and the capability of acquiring new skills even at an advanced age despite the severe initial delay.

In these cases, specific neuropsychological impairments are noted such as visuo-spatial deficits, problem-solving deficits, and language disabilities, especially evident for the morphosyntactic components (Tavano et al. 2007c). Involvement of cerebellar hemispheres in higher cognitive function as modulating thought, language, and executive abilities was described by several studies (Schmahmann 1991; Riva and Giorgi 2000). In these studies it has been hypothesized that the two hemispheres have a right-left specialization similar to that of the cerebral

hemisphere and that this inter-cerebellum specialization develops early and is consequently accompanied by a wide range of developmental disorders (Baraitser 1990; Gilbert and Coleman 1992). In particular, the right cerebellar hemisphere has a role in semantically guided word generation (Petersen et al. 1989; Petersen and Fiez 1993; Herholz et al. 1996; Fiez et al. 1992; Fabbro et al. 2004), whereas the left hemisphere plays a role in lexical access and visuospatial abilities (Silveri et al. 1993, 1998; Zettin et al. 1997; Mariën et al. 2001; Fabbro 2000; Scott et al. 2001; Fabbro et al. 2004; Tavano et al. 2007b, c). Consequently, neuropsychological and affective disorders in patients with cerebellar pathologies are likely to be a consequence of the malfunctioning of a network of complex connections (Schmahmann 2010; Bolduc et al. 2011; Salman and Tsai 2016; Stoodley 2016). These findings suggest that the volume of the cerebellar vermis and the involvement of other anatomical structures may play a significant role in cognitive functions. In addition, it has recently been demonstrated that anomalies of white matter tracts connecting the cerebellum with the brain stem and the cerebral hemispheres may also impair neurocognitive functions in children with cerebellar disorders (Poretti 2011).

These findings support the first hypothesis of Schmahmann (1991) concerning a functional topography within the cerebellum that becomes operative in an early stage. The vermis represents the cerebellar limbic system and is involved in the modulation of emotions and social behaviors, whereas the more lateral hemispheric regions are involved in cognitive behavior (modulating thought, language, and ability to plan) (Silveri et al. 1993, 1998; Botez-Marquard et al. 1994; Schmahmann and Sherman 1998; Tavano et al. 2007c). This way, it has been possible to identify different neurobehavioral patterns related to the vermal or hemispheric site of the lesions themselves.

Cases of diffuse cerebellar hypoplasia (affecting both vermis and the cerebellar hemispheres) detected by neuroimaging present a widely heterogeneous clinical picture. As previously described (Tavano et al. 2007c), in these patients, a wide-ranging clinical pattern is evident, so further neuroradiological studies are needed.

In conclusion, cerebellar agenesis, in spite of having a dramatic neuroradiological picture, is a clinical condition compatible with a productive although limited life, especially if the affected person has the opportunity to participate in a rehabilitation program at an early stage of life.

References

Aldinger KA, Doherty D (2016) The genetics of cerebellar malformations. Semin Fetal Neonatal Med 21:321–332

Aldinger KA, Lehmann OJ, Hudgins L et al (2009) FOXC1 is required for normal cerebellar development and is a major contributor to chromosome 6p24.3 Dandy-Walker malformation. Nat Genet 41:1037–1042

Alkan O, Kizilkilic O, Yildirim T (2009) Malformations of the midbrain and hindbrain: a retrospective study and review of the literature. Cerebellum 8:355–365

Al-Shammari M, Al-Husain M, Al-Kharfy T, Alkuraya FS (2011) A novel PTF1A mutation in a patient with severe pancreatic and cerebellar involvement. Clin Genet 80:196–198

Altman NR, Naidich TP, Braffman BH (1992) Posterior fossa malformations. Am J Neuroradiol 13:691–724
Anton E, Zingerle H (1914) Genaue Beschreibung eines. Falles von beiderseitigem. Kleinhimmangel. Arch Psychiatr Berl 54:8–75
Arrigoni F, Romaniello R, Nordio A et al (2015) Learning to live without the cerebellum. Neuroreport 26:809–813
Ashraf O, Jabeen S, Khan A, Shaheen F (2016) Primary cerebellar agenesis presenting as isolated cognitive impairment. J Pediatr Neurosci 11:150–152
Baker RC, Graves GO (1931) Cerebellar agenesis. Arch Neurol Psychiatr 25:548–555
Ballarati L, Rossi E, Bonati MT et al (2007) 13q deletion and central nervous system anomalies: further insights from karyotype-phenotype analyses of 14 patients. J Med Genet 44:e60
Baraitser M (1990) Cerebellar syndromes. In: Baraitser M (ed) The genetics of neurological disorders, 2nd edn. Oxford University Press, Oxford
Barkovich AJ (1998) Neuroimaging manifestations and classification of congenital muscular dystrophies. Am J Neuroradiol 19:1389–1396
Barkovich AJ, Frieden I, Williams M (1994) MR of neurocutaneous melanosis. Am J Neuroradiol 15:859–867
Barkovich AJ, Millen KJ, Dobyns WB (2007) A developmental classification of malformations of the brainstem. Ann Neurol 62:625–639
Barkovich AJ, Millen KJ, Dobyns WB (2009) A developmental and genetic classification for midbrain-hindbrain malformations. Brain 132:3199–3230
Barth PG (2000) Pontocerebellar hypoplasia-how many types? Eur J Paediatr Neurol 4:161–162
Beaton A, Mariën P (2010) Language, cognition and cerebellum: grappling with an enigma. Cortex 46(7):811–820
Bellini C, Massocco D, Serra G (2000) Prenatal cocaine exposure and the expanding spectrum of brain malformations. Arch Intern Med 160:2393
Boland E, Clayton-Smith J, Woo VG et al (2007) Mapping of deletion and translocation breakpoints in q44 implicates the serine/threonine kinase AKT3 in postnatal microcephaly and agenesis of corpus callosum. Am J Hum Genet 81:292–303
Bolduc ME, Du Plessis AJ, Sullivan N (2011) Spectrum of neurodevelopmental disabilities in children with cerebellar malformations. Dev Med Child Neurol 53:409–416
Boltshauser E (2004) Cerebellum-small brain but large confusion: a review of selected cerebellar malformations and disruptions. Am J Med Genet 126A:376–385
Boltshauser E (2008) Cerebellar hypoplasias. Disorders of segmentation of the neural tube. In: Handbook of clinical neurology, vol 87 (3rd series). Malformation of the nervous system (Ed Elsevier)
Borgatti R, Tavano A, Cristofori G et al (2004) Language development in children with cerebellar malformations. In: Fabbro F (ed) Neurogenic language disorders in children. Elsevier, Amsterdam
Borrell H (1884) Cerebellar agenesis. Arch f Psychiatr 15:286
Bosemani T, Poretti A (2016) Cerebellar disruptions and neurodevelopmental disabilities. Semin Fetal Neonatal Med 21:339–348
Botez-Marquard T, Leveillé J, Botez MI (1994) Neuropsychological functioning in unilateral cerebellar damage. Can J Neurol Sci 21:353–357
Boyd JD (1940) A case of neocerebellar hypoplasia. J Anat 74:557
Boyd CA (2009) Cerebellar agenesis revisited. Brain 133:941–944
Brielmaier J (2016) The woman born without a cerebellum: a real-life case adapted for use in an undergraduate developmental and systems neuroscience course. J Undergrad Neurosci Educ 15(1):C1–C3. eCollection 2016 Fall
Buckner RL (2013) The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. Neuron 80:807–815
Casartelli L, Federici A, Cesareo A et al (2017) Role of the cerebellum in high stages of motor planning hierarchy. J Neurophysiol 117:1474–1482
Casartelli L, Riva M, Villa L, Borgatti R (2018) Insights from perceptual, sensory, and motor functioning in autism and cerebellar primary disturbances: are there reliable markers for these disorders? Neurosci Biobehav Rev 95:263–279

Chang B, Piao X, Bodell A et al (2003) Bilateral frontoparietal polymicrogyria: clinical and radiological features in 10 families with linkage to chromosome 16. Ann Neurol 53:596–606
Chedda MG, Sherman JC, Schmahmann JD (2002) Neurology, psychiatric and cognitive manifestations in cerebellar agenesis. Neurology 58:A356
Chen CP, Chen CP, Shih JC (2005) Association of partial trisomy 9p and the Dandy Walker malformation. Am J Med Genet 132A:111–112
Clouchoux C, Guizard N, Evans AC et al (2012) Normative fetal brain growth by quantitative in vivo magnetic resonance imaging. Am J Obstet Gynecol 206:173.e1e8
Cohen I (1942) Agenesis of the cerebellum (verified by operation). J Mt. Sinai Hosp 8:441–446
Combettes M (1831) Absence complète du cervelet, des pédoncules postérieurs et de la protubérance cérébrale chez une jeune fille morte dans sa onzième anneé. Bull Soc Anat de Paris 5:148–157
Cordes SP (2001) Molecular genetics of cranial nerve development in mouse. Nat Rev Neurosci 2:611–623
Cotes C, Bonfante E, Lazor J et al (2015) Congenital basis of posterior fossa anomalies. Neuroradiol J 28:238–253
Courchesne E (1997) Brainstem, cerebellar and limbic neuroanatomical abnormalities in autism. Curr Opin Neurobiol 7:269–278
Courchesne E, Townsend J, Akshoomoff NA et al (1994) Impairment in shifting attention in autistic and cerebellar patients. Behav Neurosci 108:848–865
D'Mello AM, Stoodley CJ (2015) Cerebro-cerebellar circuits in autism spectrum disorder. Front Neurosci 9:408
Dahlem K, Valko Y, Schmahmann JD, Lewis RF (2016) Cerebellar contributions to self-motion perception: evidence from patients with congenital cerebellar agenesis. J Neurophysiol 115:2280–2285
Davis EE, Pitchford NJ, Jaspan T et al (2010) Development of cognitive and motor function following cerebellar tumour injury sustained in early childhood. Cortex 46:919–932
Dhillon AS, Chapman S, Milford DV (2001) Cerebellar defect associated with Schimke immune-osseous dysplasia. Eur J Pediatr 160:372–274
Doherty D, Millen KJ, Barkovich AJ (2013) Midbrain and hindbrain malformations: advances in clinical diagnosis, imaging, and genetics. Lancet Neurol 12:381–393
Fabbro F (2000) Introduction to language and cerebellum. J Neurolinguistics 13:83–94
Fabbro F, Tavano A, Corti S et al (2004) Long-term neuropsychological deficits after cerebellar infarctions in two young twins. Neuropsychologia 42:536–545
Ferrier D (1876) The functions of the brain, Chapter VI. In: Functions of the cerebellum. Smith, Elder, London
Fiez JA, Petersen SE, Cheney MK et al (1992) Impaired non-motor learning and error detection associated with cerebellar damage. Brain 115:155–168
Freeze HH (2001) Update and perspective on congenital disorders of glycosylation. Glycobiology 11:129R–143R
Fusari R (1891) Note sur quelques cas d'atrophie et d'hypertrophie du cervelet. Mem v Accad d sc d Inst Bologna 2:643–658
Gabbay M, Ellard S, De Franco E, Moisés RS (2017) Pancreatic agenesis due to compound heterozygosity for a novel enhancer and truncating mutation in the *PTF1A* gene. J Clin Res Pediatr Endocrinol 9:274–277
Gardner RJM, Coleman LT, Mitchell LA et al (2001) Near-total absence of the cerebellum. Neuropediatrics 32:62–68
Gelal FM, Kalaycı TÖ, Çelebisoy M (2016) Clinical and MRI findings of cerebellar agenesis in two living adult patients. Ann Indian Acad Neurol 19:255–257
Gilbert C, Coleman M (1992) The biology of the autistic syndromes. McKeit Press, London
Glickstein M (1994) Cerebellar agenesis. Brain 117:1209–1212
Goldowitz D, Hamre K (1998) The cells and molecules that make a cerebellum. Trends Neurosci 21:375–382
Gordon N (2007) The cerebellum and cognition. Eur J Paediatr Neurol 11:232–234

Grinberg I, Millen KJ (2005) The ZIC gene family in development and disease. Clin Genet 67:290–296
Herholz K, Thiel A, Wienhard W et al (1996) Individual functional anatomy of verb generation. NeuroImage 3:185–194
Hill AD, Chang BS, Hill RS et al (2007) A 2-Mb critical region implicated in the microcephaly associated with terminal 1q deletion syndrome. Am J Med Genet 143A:1692–1698
Hong SE, Shugart YY, Huang DT et al (2000) Autosomal recessive lissencephaly with cerebellar hypoplasia (LCH) is associated with human reelin gene mutations. Nat Genet 26:93–96
Houghton JA, Swift GH, Shaw-Smith C et al (2016) Isolated pancreatic aplasia due to a hypomorphic PTF1A mutation. Diabetes 65:2810–2815
Hoveyda N, Shield JP, Garrett C et al (1999) Neonatal diabetes mellitus and cerebellar hypoplasia/agenesis: report of a new recessive syndrome. J Med Genet 36:700–704
Huissoud C, Rudigoz RC, Bisch C et al (2009) Complete cerebellar agenesis: a very rare abnormality of the posterior fossa. Ultrasound Obstet Gynecol 33:730–731
Jacob FD, Goez HR (2011) Preservation of language in the ataxic infant in a case of cerebellar agenesis. Can J Neurol Sci 38:143–144
Jalali A, Aldinger J, Chary A et al (2008) Linkage to chromosome 2q36.1 in autosomal dominant Dandy-Walker malformation with occipital cephalocele and evidence for genetic heterogeneity. Hum Genet 123:237–245
Jansen A, Floel A, Van Randenborgh J et al (2005) Crossed cerebro-cerebellar language dominance. Hum Brain Mapp 24:165–172
Karmiloff-Smith A (1995) Beyond modularity: a developmental perspective on cognitive science. MIT Press, Cambridge, MA
Kier G, Winchester BG, Clayton P (1999) Carbohydrate deficient glycoprotein syndromes: inborn errors of protein glycosylation. Ann Clin Biochem 36:20–36
Kim SG, Ugurbil K, Strick PL (1994) Activation of a cerebellar output nucleus during cognitive processing. Science 265:949–951
Kirschen MP, Davis-Ratner MS, Milner MW (2008) Verbal memory impairments in children after cerebellar tumor resection. Behav Neurol 20:39–53
Laforce R Jr, Doyon J (2001) Distinct contribution of the striatum and cerebellum to motor learning. Brain Cogn 45:189–211
Laforce R Jr, Doyon J (2002) Differential role for the striatum and cerebellum in response to novel movements using a motor learning paradigm. Neuropsychologia 40:512–517
Leech RW, Johnson SH, Brumback RA (1997) Agenesis of cerebellum associated with arhinencephaly. Clin Neuropathol 16:90–97
Leestma JE, Torres JV (2000) Unappreciated agenesis of cerebellum in an adult. Am J of Forensic Med Pathol 21:155–161
Leiner HC, Leiner AL, Dow RS (1991) The human cerebro-cerebellar system: its computing, cognitive and language skills. Behav Brain Res 44:113–128
Lemon RN, Edgley SA (2010) Life without a cerebellum. Brain 133:652–654
Leto K, Arancillo M, Becker EB (2016) Consensus paper: cerebellar development. Cerebellum 15:789–828
Levisohn L, Cronin-Golomb A, Schmahmann JD (2000) Neuropsychological consequences of cerebellar tumor resection in children: cerebellar cognitive affective syndrome in a paediatric population. Brain 123:1041–1050
Leyden E (1876) Citation in Stewart RM (1956) Cerebellar agenesis. J Ment Sci 102:67–77
Limperopoulos C, Soul JS, Gauvreau K et al (2005) Late gestation cerebellar growth is rapid and impeded by premature birth. Pediatrics 115:688–695
Limperopoulos C, Bassan H, Gauvreau K et al (2007) Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? Pediatrics 120:584–593
Limperopoulos C, Chilingaryan G, Guizard N et al (2010) Cerebellar injury in the premature infant is associated with impaired growth of specific cerebral regions. Pediatr Res 68:145–150

Loeser JD, Lemire RJ, Alvord J (1972) The development of the folia in the human cerebellar vermis. Anat Rec 173:109–114
Mariën P, Engelborghs S, Fabbro F et al (2001) The lateralized linguistic cerebellum: a review and a new hypothesis. Brain Lang 79:580–600
McCormack WM, Shen JJ, Curry SM et al (2003) Partial deletions of the long arm of chromosome 13 associated with holoprosencephaly and the Dandy-Walker malformation. Am J Med Genet 118:384–389
Melaragno MI, Brunoni D, Patricio FR et al (1992) A patient with tetrasomy 9p, Dandy-Walker cyst and Hirschsprung disease. Ann Genet 35:79–84
Meola A, Fernandez-Miranda JC (2015) Peduncles without cerebellum: the cerebellar agenesis. Eur Neurol 74(3–4):162. https://doi.org/10.1159/000441055. Epub 2015 Oct 10
Micalizzi A, Poretti A, Romani M (2016) Clinical, neuroradiological and molecular characterization of cerebellar dysplasia with cysts (Poretti-Boltshauser syndrome). Eur J Hum Genet 24:1262–1267
Millen KJ, Gleeson JG (2008) Cerebellar development and disease. Curr Opin Neurobiol 18:12–19
Millen KJ, Steshina EY, Iskusnykh IY, Chizhikov VV (2014) Transformation of the cerebellum into more ventral brainstem fates causes cerebellar agenesis in the absence of Ptf1a function. Proc Natl Acad Sci U S A 111:E1777–E1786
Miyata H, Chute DJ, Fink J et al (2004) Lissencephaly with agenesis of corpus callosum and rudimentary dysplastic cerebellum: a subtype of lissencephaly with cerebellar hypoplasia. Acta Neuropathol 107:69–81
Moberget T, Andersson S, Lundar T et al (2015) Long-term supratentorial brain structure and cognitive function following cerebellar tumour resections in childhood. Neuropsychologia 69:218–231
Mormina E, Briguglio M, Morabito R (2016) A rare case of cerebellar agenesis: a probabilistic constrained spherical deconvolution tractographic study. Brain Imaging Behav 10:158–167
Murdoch BE (2010) The cerebellum and language: historical perspective and review. Cortex 46(7):858–868
Najm J, Horn D, Wimplinger I et al (2008) Mutation of CASK cause an X-linked brain malformation phenotype with microcephaly and hypoplasia of the brainstem and cerebellum. Nat Genet 40:1065–1067
Niesen CE (2002) Malformations of the posterior fossa: current perspectives. Semin Pediatr Neurol 9:320–334
Nowak DA, Timmann D, Hermsdorfer J (2007) Dexterity in cerebellar agenesis. Neuropsychologia 45:696–703
Oegema R, Cushion TD, Phelps IG et al (2015) Recognizable cerebellar dysplasia associated with mutations in multiple tubulin genes. Hum Mol Genet 24:5313–5325
Parisi MA, Dobyns WB (2003) Human malformations of the midbrain and hindbrain: review and proposed classification scheme. Mol Genet Metab 80:36–53
Patel S, Barkovich AJ (2002) Analysis and classification of cerebellar malformations. Am J Neuroradiol 23:1074–1087
Petersen SE, Fiez JA (1993) The processing of single words studied with positron emission tomography. Annu Rev Neurosci 16:509
Petersen SE, Fox PT, Posner MI et al (1989) Positron emission tomographic studies of the processing of single words. J Cogn Neurosci 1:153–170
Philphot J, Pennock J, Cowan F et al (2000) Brain magnetic resonance imaging abnormalities in merosin-positive congenital muscular dystrophy. Eur J Paediatr Neurol 4:109–114
Poretti A (2011) Cognitive functions in children with cerebellar malformations. Dev Med Child Neurol 53:389
Poretti A, Boltshauser E (2015) Terminology in morphological anomalies of the cerebellum does matter. Cerebellum Ataxias 2:8
Poretti A, Boltshauser E, Huisman TA (2016) Cerebellar and brainstem malformations. Neuroimaging Clin N Am 26:341–357

Poretti A, Prayer D, Boltshauser E (2009) Morphological spectrum of prenatal cerebellar disruption. Eur J Paediatr Neurol 13:397–407
Poretti A, Risen S, Meoded A et al (2013) Cerebellar agenesis: an extreme form of cerebellar disruption in preterm neonates. J Pediatr Neuroradiol 2:163–167
Poretti A, Wolf NI, Boltshauuser E (2008) Differential diagnosis of cerebellar atrophy in childhood. Eur J Paediatr Neurol 12(3):155–167
Priestly DP (1920) Complete absence of the cerebellum. Lancet 2:1302
Reardon W, Donnai D (2007) Dysmorphology demystified. Arch Dis Child Fetal Neonatal Ed 92: F225–F229
Riccardi VM, Marcus ES (1978) Congenital hydrocephalus and cerebellar agenesis. Clin Genet 13:443–447
Richter S, Dimitrova A, Hein-Kropp C et al (2005) Cerebellar agenesis II: motor and language functions. Neurocase 11:103–113
Riva D, Giorgi C (2000) The cerebellum contributes to higher functions during development. Evidence from a series of children surgically treated for posterior fossa tumors. Brain 123:1051–1061
Romaniello R, Arrigoni F, Panzeri E et al (2017) Tubulin-related cerebellar dysplasia: definition of a distinct pattern of cerebellar malformation. Eur Radiol 27:5080–5092
Ronconi L, Casartelli L, Carna S et al (2017) When one is enough: impaired multisensory integration in cerebellar agenesis. Cereb Cortex 27:2041–2051
Ross ME, Swanson K, Dobyns WB (2001) Lissencephaly with cerebellar hypoplasia (LCH): a heterogeneous group of cortical malformations. Neuropediatrics 32:256–263
Salman MS, Tsai P (2016) The role of the pediatric cerebellum in motor functions, cognition, and behavior: a clinical perspective. Neuroimaging Clin N Am 26:317–329
Schmahmann ID (1991) An emerging concept: the cerebellar contribution to higher function. Arch Neurol 48:1178–1187
Schmahmann JD (1996) From movement to though: anatomic substrates of the cerebellar contribution to cognitive processing. Hum Brain Mapp 4:174–198
Schmahmann JD (1997) The cerebellum and cognition. Int Rev Neurobiol, vol 41. Academic Press, San Diego
Schmahmann JD (2010) The role of the cerebellum in cognition and emotion: personal reflections since 1982 on the dysmetria of thought hypothesis, and its historical evolution from theory to therapy. Neuropsychol Rev 20:236–260
Schmahmann JD, Sherman JC (1998) The cerebellar cognitive affective syndrome. Brain 121:561–579
Schmahmann JD, Weilburg JB, Sherman JC (2007) The neuropsychiatry of the cerebellum – insights from the clinic. Cerebellum 6:254–267
Scott RB, Stoodley CJ, Anslow P et al (2001) Lateralized cognitive deficits in children following cerebellar lesions. Dev Med Child Neurol 43:685–691
Sellick GS, Barker KT, Stolte-Dijkstra I et al (2004) Mutations in PTF1A cause pancreatic and cerebellar agenesis. Nat Genet 36:1301–1305
Sener RN (1995) Cerebellar agenesis versus vanishing cerebellum in Chiari II malformation. Comput Med Imaging Graph 19:491–494
Sener RN, Jinkins JR (1993) Subtotal agenesis of the cerebellum in an adult. MRI demonstration. Neuroradiology 35:286–287
Silveri C, Leggio MG, Molinari M (1993) The cerebellum contributes to language production: a case of agrammatic speech following a right cerebellar lesion. Neurology 44:2047–2050
Silveri MC, Di Betta AM, Filippini V et al (1998) Verbal short-term store-rehearsal system and the cerebellum. Evidence from a patient with a right cerebellar lesion. Brain 121:2175–2187
Squier W, Hope PL, Lindenbaum RH (1990) Neocerebellar hypoplasia in a neonate following intrauterine exposure to anticonvulsivants. Dev Med Child Neurol 32:737–742
Steinlin M, Zangger B, Boltshauser E (1998) Non-progressive congenital ataxia with or without cerebellar hypoplasia: a review of 34 subjects. Dev Med Child Neurol 40:148–154
Steinlin M, Styger M, Boltshauser E (1999) Cognitive impairments in patients with congenital nonprogressive cerebellar ataxia. Neurology 53:966–973

Sternberg C (1912) Ueber vollstandigen Defekt des Kleinhirnes. Verhandl Deutsch Path Gesellsch 15:359–363
Stewart RM (1956) Cerebellar agenesis. J Ment Sci 102:67–77
Stoodley CJ (2016) The cerebellum and neurodevelopmental disorders. Cerebellum 15:34–37
Stoodley CJ, Limperopoulos C (2016) Structure-function relationships in the developing cerebellum: evidence from early-life cerebellar injury and neurodevelopmental disorders. Semin Fetal Neonatal Med 21(5):356–364
Tavano A, Borgatti R (2010) Evidence for a link among cognition, language and emotion in cerebellar malformations. Cortex 46(7):907–918
Tavano A, Fabbro F, Borgatti R (2004) Speaking without the cerebellum. Proct Int Lang Cogn Conf offs Harbour
Tavano A, Fabbro F, Borgatti R (2007a) Speaking without the cerebellum: language skills in a young adult with near total absence of the cerebellum. In: Schalley A, Khlentzos D (eds) Mental states: evolution, function, nature. John Benjamin, Amsterdam
Tavano A, Fabbro F, Borgatti R (2007b) Language and social communication in children with cerebellar dysgenesis. Folia Phoniatr Logop 59:201–209
Tavano A, Grasso R, Gagliardi C et al (2007c) Disorders of cognitive and affective development in cerebellar malformations. Brain 130:2646–2660
Tennstedt A (1965) Kleinhirnaplaise beim Erwachsenen. Zentralbl Allg Pathol 107:301–304
Thach TW (1997) Context-response linkage. Int Rev Neurobiol 41:599–611
Timmann D, Dimitrova A, Hein-Kropp C et al (2003) Cerebellar agenesis: clinical, neuropsychological and MR findings. Neurocase 9(5):402–413
Timmann D, Drepper J, Frings M et al (2010) The human cerebellum contributes to motor, emotional and cognitive associative learning: a review. Cortex 46:845–857
Titomanlio L, Romano A, Del Giudice E (2005) Cerebellar agenesis. Neurology 64:E21
Titomanlio L, De Brasi D, Romano A et al (2006) Partial cerebellar hypoplasia in a patient with Prader-Willi syndrome. Acta Paediatr 95:861–863
Tutak E, Satar M, Yapicioglu H et al (2009) A Turkish newborn infant with cerebellar agenesis/neonatal diabetes mellitus and PTF1A mutation. Genet Couns 20(2):147–152
Uhl M, Pawlik H, Laudenberger J et al (1998) MR findings in pontocerebellar hypoplasia. Pediatr Radiol 28:547–551
Ullman M (1997) A neural dissociation within language: evidence that mental dictionary is part of declarative memory, and that grammatical rules are processed by the procedural system. J Cogn Neurosci 9:266–276
Van Bon BW, Koolen DA, Borgatti R et al (2008) Clinical and molecular characteristics of 1qter microdeletion syndrome: delineating a critical region for corpus callosum agenesis/hypogenesis. J Med Genet 45:346–254
Van Coster RN, De Praeter CM, Vanhaesebrouck PJ et al (1998) MRI finding in a neonate with cerebellar agenesis. Pediatr Neurol 19:139142
Van Hoof SC, Wilmink JT (1996) Cerebellar agenesis. J Belg Radiol 79:282
Velioglu SK, Kuzelyli K, Zzmenoglu M (1998) Cerebellar agenesis: a case report with clinical MR imaging finding and a review of the literature. Eur J Neurol 5:503–506
Verdelli A (1874) Citation in Stewart RM (1956) Cerebellar agenesis. J Ment Sci 102:67–77
Wang SSH, Kloth AD, Badura A (2014) The cerebellum, sensitive periods, and autism. Neuron 83:518–532
Yu F, Jiang QJ, Sun XY, Zhang RW (2015) A new case of complete primary cerebellar agenesis: clinical and imaging findings in a living patient. Brain 138(Pt 6):e353
Zaferiou DI, Vargiami E, Bolthsauser E (2004) Cerebellar agenesis and diabetes insipidus. Neuropediatrics 35:364–367
Zanni G, Saillour Y, Nagara M et al (2005) Oligophrenin 1 mutations frequently cause X-linked mental retardation with cerebellar hypoplasia. Neurology 65:1364–1369
Zettin M, Cappa SF, D'Amico A et al (1997) Agrammatic speech production after a right cerebellar haemorrhage. Neurocase 3:375–380