# 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 disorders of affect. Severity and range of motor, cognitive, and psychiatric impairments appears to be correlated with earliness, localization, and extent of the agenesis of cerebellum. Patients with congenital malformations present indeed a more severe and less specific impairment than patients with acquired cerebellar lesions in adult life. Patients with involvement of the phylogenetically most ancient structures (complete or partial cerebellar vermis agenesis) show the more severe clinical picture, in particular severe pervasive impairments in social and communication skills (autism or autistic-like behavior), in behavior modulation (self-injury and aggressiveness), and markedly delay 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 extraordinary neuroradiological picture, is a clinical condition compatible with an honorable existence, although limited, especially if the affected person has the opportunity to undergo a rehabilitation program at an early stage of his life.

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Significant progresses were made during the past 2 decades in the study of posterior fossa disorders thanks to the improvement in neuroimaging techniques and through the development of specific diagnostic protocols. However, several issues still need to be addressed for example, the distinction between agenesis, hypoplasia, or atrophy. As evidence of the confusing data presenting in the international literature, an important Author as Boltshauser entitles his review on this topic "Cerebellum-Small Brain But Large Confusion" (Boltshauser 2004).

The term *agenesis* means the partial or almost complete lack of cerebellum while *hypoplasia* is the condition in which cerebellar vermis, hemisphere or both normally exist but with small in size (Bolthshauser 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 shrank cerebellum) (Poretti et al. 2008). In clinical practice distinction is not so easy, especially in the absence of the comparison of 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 the majority of patients had considerable cerebellar tissue, found postmortem or by neuroimaging (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 is not compatible with life, as it 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 designation "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 brainstem, showing marked pontine hypoplasia, and a collection of cerebrospinal fluid which passively fills the space normally occupied by cerebellum.

Clinical presentation of cerebellar agenesis may cover a broad phenotypic spectrum of disabilities regarding motor, cognitive, affective impairment differently mixed and with a wide range of severity.

The aim of this chapter is twofold: first to review and to summarize recent embryological, physiopathogenic, and classification proposal of cerebellar agenesis

for a better comprehension of these conditions; second, to resume clinical cases previously described in literature or personally observed to document 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 3 and 5 weeks of gestation, the neural tube bends at the cranial and cervical flexures and the rhombencephalon subdivides into eight rhombomeres (Niesen 2002). Thereafter, 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 zones form 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 fourth ventricle, the roof of which develops into the cerebellum. Between 6 and 7 weeks 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 giving rise to 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 4 months of gestation, while development of the large cerebellar hemispheres (neocerebellum) lags behind that of the vermis by 30–60 days (Altman et al. 1992). Postnatal, proliferation of the cellular components of the cerebellum continues, 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 about 20 months 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).

These findings suggest that highly complex biological processes underlie midbrain–hindbrain and cerebellum development, extending in time beyond the birth, consequently determining a strong vulnerability of these structures to several both genetic and environmental factors.

## Pathological Mechanisms of Cerebellar Anomalies

Recently the growing use and the increasing improvement of neuroimaging techniques allowed the identification and the description with great accuracy of developmental anomalies of the structures of the posterior fossa and particularly of the cerebellum (Boltshauser 2004, 2008). Nevertheless, some difficulties remain for definite and precise categorization of the clinical picture observed as secondary to a congenital malformation or as a result of 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 likely appear to represent a morphological spectrum. A clear classification of these patterns remains difficult to achieve. It is to be 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 counseling (Poretti et al. 2009).

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 could contribute to susceptibility to disruption (Boltshauser 2008; Poretti et al. 2009). 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, cerebellar malformations are associated with more complex brain malformations genetically determined such as lissenchephaly (Ross et al. 2001; Miyata et al. 2004), bilateral frontoparietal plymicrogiria due to mutations of GPR56 gene (Chang et al. 2003), malformation of cortical development due to RELN gene (Hong et al. 2000), some types of congenital muscular dystrophies (Barkovich 1998; Philphot et al. 2000), and pontocerebellar hypoplasia (Uhl et al. 1998; Barth 2000). Recently, a mutation in PTF1A gene (10p12.3 locus) was described (Sellick et al. 2004; Millen and Gleeson 2008; Tutak et al. 2009) in

patients with cerebellar agenesis and diabetes mellitus. These genes expressed in the cerebellar ventricular zone play a crucial role in cerebellar GABAergic neuronal specification and cerebellar neurogenesis. In 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 because their GABAergic synaptic partners are not present. Among metabolic disorders (Steinlin et al. 1998), the most important are the 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 (Bellini et al. 2000) exposure, intrauterine death of one fetus in a monochorionic twin pregnancy, 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 developing cerebellum. Unilateral cerebellar aplasia (UCA) may be the result of a unilateral disruptive event, whereas an early bilateral disruptive event could be considered as an explanation for cerebellar agenesis (Boltshauser 2004). Only occasional findings show unilateral cerebellar hypoplasia (CH) or aplasia associated with a complex brain malformation such as holoprosencephaly (Poretti et al. 2009) or with syndromic pictures (Dhillon et al. 2001; Titomanlio et al. 2006). Cerebellar agenesis is also described in patients affected by prenatal infections, particularly cytomegalovirus (CMV) with an indirect role in inducing neuronal loss by apoptosis and by activating neuroinflammatory responses. Such an event occurring around 24 weeks 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).

## Classification Systems

In the course of the years, few 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. 2009). In fact, because of the heterogeneity of malformations and the prolonged period of development of cerebellum, it is very difficult to understand the pathogenesis of cerebellar malformations and the correlation between the morphological and ontogenetic subdivisions.

The classification system of Parisi and Dobyns (2003) and more recently of Barkovich et al. (2009) tried an approach to relate malformations to the embryological structures involved, 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 relationship and to clarify these groups of disorders. Moreover, the flexibility of these

classifications should facilitate the description of new embryologic processes or the discovery of novel malformations.

Accordingly, the classification system of Barkovich et al. (2009) considers that midbrain and hindbrain malformations are divided in four groups: malformations secondary to early anteroposterior and dorsoventral patterning defects; malformations associated with later generalized developmental disorders that significantly affect the brainstem and cerebellum; localized brain malformations that significantly affect the brain stem and cerebellum; combined hypoplasia and atrophy in putative prenatal onset degenerative disorders. Noticeable distribution of malformation within each group can be changed as 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 in a systematic approach.

Cerebellar malformations can be gathered into two broad categories distinguished by the presence of hypoplasia versus dysplasia. Cerebellar hypoplasia (CH) is further subdivided in focal hypoplasia (isolated vermis hypoplasia and hemisphere hypoplasia) and in 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 as the complete unilateral cerebellar aplasia (UCA) (unilateral absence of a cerebellar hemisphere). Nevertheless, the hypothesis about the acquired disruptive process underlying UCA requires caution, in particular in placing "one hemisphere hypoplasia" as a cerebellar malformation in the scheme proposed by Patel and Barkovich (2002) (Boltshauser 2004). Of note, the severity of the cerebellar abnormalities usually correlates with the timing of the disruption during the pregnancy.

## Case Reports

### 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 a 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 showing severe clinical picture, always associated with other brain malformations or with complex syndromes, with fatal exit within the first days or weeks of life. There are only 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 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 near total cerebellar agenesis in the context of a complex syndrome, associated with presumably X-linked hydrocephalus, who died on 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. The description by Leech et al. (1997), van Coster et al. (1998) of some cases with similar findings allowed Sellick et al. (2004) to identify the genetic mechanism underlying this syndrome, mutation in PTF1A gene, subsequently confirmed by Millen and Gleeson (2008), and by Tutak et al. (2009).

Cases described in the literature with cerebellar agenesis surviving until adulthood are quite rare. The first instance 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 by 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 delay development (she learned to walk and to speak at the age of 6, started school at 10 learning to reading and writing). Anton and Zingerle (1914) reported a girl who learned to walk at 4 years and to speak at the age of 5. Developmental deficits like these are described in other single case descriptions by Baker and Graves (1931), Boyd (1940), Cohen (1942), Tennstedt (1965). Particularly rich and well documented is the history described by Stewart (1956) about a man surviving until the age of 55 in whom the 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 owing to the large size of his head, appeared evidently abnormal since birth. It is unknown at what age he started to crawl 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 had frequent falls but was able to climb stairs unaided. Speech was acquired late and articulation, although gradually improving over the years, never became distinct. In spite of his obvious mental retardation, he remained at an 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.

During his life, he became progressively more responsible even though he never became independent. After the death of his parents, he was received in an institution. His clinical condition remained stable for a long time, and worsened dramatically only during the last year of life when he lost the ability to walk and move.

Glickstein (1994) has reviewed all the literature on these historical cases, focusing in particular on the case already described by Boyd (1940). He aimed to refuse the oral tradition, 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) concludes that people born without cerebellum are profoundly impaired in motor development

and during life they are slow in walking and talking and remain always very clumsy. The same conclusions were reached by the authors who have studied in a sophisticated manner and with modern techniques of investigation cases of recent observation. The case reported by Timman and her group (Timmann et al. 2003; Richter et al. 2005; Nowak et al. 2007) is pathognomonic. 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 clumsy with her hands. Development of speech was delayed. Speech was slow and slurred. The lack of coordination is described to have slightly improved over the years. At the age of 7, she started to attend a regular school but she never learnt to read and write apart from her name. After leaving school, she started to work in the farm of her parents. She was able to help by working, and she learnt to ride a bicycle. Following a car accident, she severely injured the right hip, and consequently she was forced to stop working in the farm and starting to work in the electronics department in a workshop for disabled people. This patient became able to connect cables with lamps and to screw plugs without significant impairment. She never got married and lived in her own, lodging in one of her brother's places. 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 executive, visuospatial, and language tasks were found.

Among the publications of the last 2 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), other cases have been described, in whom, although they have been studied with less details, it has been confirmed that a nearly total absence of the cerebellum may cause many clinical symptoms even if features and severity can be variable. The motor disturbances affect walking, writing, and articulation of speech. Intellectual disabilities cause learning difficulties and limit the autonomy. Often these patients cannot live without assistance. In addition, it is interesting to note that more and more frequently delayed developmental milestone is reported, with a trend toward improvement over time.

These findings are in line with the emerging concept that cerebellum does play 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 supporting the role of 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, 2010; Schmahmann and Sherman 1998; Fabbro 2000; Gordon 2007; Beaton and Mariën 2010; Murdoch 2010) and a role as center for higher cognitive function as well. The complex set of symptoms exceeding the simple motor deficit was first synthesized as "Cerebellar Cognitive-Affective Syndrome" (CCAS) by Schmahmann and Sherman (1998) who described adults patients with acquired cerebellar lesions showing impairment

of executive functions, visuospatial disorganization, affect changes, expressive speech/language deficits (agrammatism, mild anomia, dysprosodia). These data were subsequently confirmed by Levisohn et al. (2000) and Riva and Giorgi (2000) for a pediatric population with acquired cerebellar lesions and from Chedda et al. (2002) and Tavano et al. (2007c) in children with cerebellar malformations.

## Personal Case

According with all these data of the literature are the clinical features showed by the subject RG, presenting near total cerebellar agenesis, followed in our Scientific Institute since the age of 4 and previously described in research papers (Borgatti et al. 2004; Tavano et al. 2007a, b, c). At the time of the last evaluation, he is a 41-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 2,500 g. Since the first month of life, he had shown 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. At the relational level, until the 4th year of life he was described as a very isolated child, 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. Also, language development was delayed (says two clear words: 24 months, uses nine clear words: 5 years, uses two words or longer sentences: 6 years, uses more two 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 at our Institute where he lived during the school year. Since then RG has always been followed by rehabilitation centers of our Institute, thus allowing us to retrace in detail his life history and witness 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 to plan the task and reinforced him at the attentional level. 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 of our Institute where he still lives today in the framework of a rehabilitation program centered on learning of basic self-sufficiency skills. Today, at the age of 45, RG is completely independent in his personal life, performs a simple job (assembles electrotechnical parts), knows the value of money, is

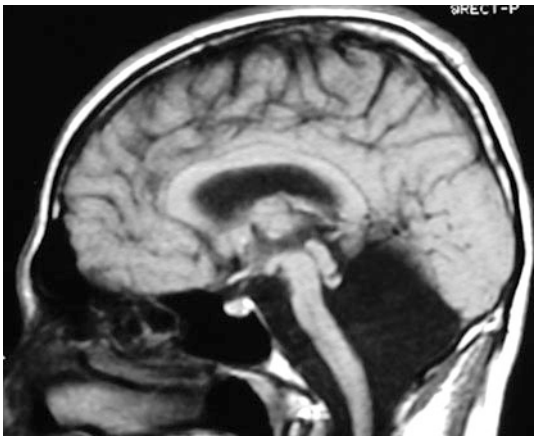

**Fig. 84.1** MRI examination: midsagittal T1-weighted 4 mm thick sections. Normal sized posterior fossa with an almost completely absent vermis. A small 3–4 mm remnant is visible in the region of the superior velum medullaris and lingula. The fourth ventricle is absent and the pons is clearly hypoplastic. Cerebral hemisphere and diencephalic structures do not show abnormalities

able to go shopping; 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. 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 of Lombardy) he takes a bus to a big city (Bergamo) where he stops for some hours during which he has lunch (choosing from time to time among several alternatives: small restaurants, pizza houses, cafés) or shops for himself or for friends he will be visiting. At the age of 31, brain MRI demonstrates a total cerebellar aplasia with normal development of the posterior cranial fossa (Fig. 84.1). A detailed neurologic and neuropsychological assessment was performed to describe the compensatory mechanisms he developed and his motor and cognitive residual deficits. Data are reported in Table 84.1.

The neuropsychological assessment documents an end-state harmonious profile of mild retardation (VIQ = 72, PIQ = 67, FIQ = 68); subtests requiring procedural motor efficiency (Coding), procedural memory of operations (Arithmetic), the extraction of higher-order semantic inferences (Similarities) and visuospatial abilities (Picture Arrangement) are the most impaired. As for visuospatial abilities, no signs of constructional apraxia were present. Thus, the highly severe impairment on the Rey Complex Figure Test cannot be preeminently attributed to peripheral graphomotor disturbances. Actually, as shown in Schmahmann and Sherman (1998) and Borgatti et al. (2004), this finding is likely to represent a major inability to appreciate the organizing structure of the figure. Alternatively, such findings could be attributed to executive (planning and attention) difficulties, given the evidence that the cerebellum participates in sustaining the frontal lobe functions (Courchesne et al. 1994). The Tower of London Test results are in agreement with this hypothesis. However, the fact that the patient performed within normal limits on the Wisconsin Card Sorting Test shows that RG does not suffer from frontal symptoms, such as perseveration. Therefore, RG seems to be impaired on tasks

**Table 84.1** Neurological and neuropsycological assessment

| | | | |
|---|---|---|---|
| *Neurological Assessment*[a] | | | |
| I. Posture and gait disturbances | | 8/34 | (23.5% of disruption) |
| II. Kinetic functions | | 16/52 | (30% of disruption) |
| III. Speech disorders | | 3/8 | (37% of disruption) |
| IV. Oculomotor disorders | | 2/6 | (33% of disruption) |
| *Total Ataxia Score* | | 29/100 | (29% of disruption) |
| *Intelligence and executive functions* | | | |
| WAIS | VIQ | 72 | |
| | PQI | 67 | |
| | FIQ | 68 | |
| Wisconsin card sorting test | | 79/98 | (Normal values) |
| Tower of London | | 8.62 | (<2SD) |
| Rey copy | | 23.5 | (<4SD) |
| Barrage test | | 40 | (<2SD) |
| *Memory* | | | |
| Spatial | | | |
| Corsi | | 4 | (<1SD) |
| Rey short memory | | 16.5 | (<1SD) |
| Rey long memory | | 17 | (<1SD) |
| Short-term verbal memory | | Four disyllabic words | |
| Long-term verbal memory (story) | | 8.5 | (<2SD) |
| *Language*[b] | | | |
| Spontaneous speech | Fluency | Ninety words/min (normal value 110 words/min) | |
| | MLU | Six words/utterance | |
| | Errors | inflectional morphology | |
| Linguistic skills | Comprehension | 78% (of correct answers) | |
| | Repetition | 100% | |
| | Judgment | 98% | |
| | Lexical access | 92% | |
| | Propositioning | 86% | |
| | Reading | 89% | |
| | Writing | 60% | |
| Linguistic levels | Phonology | 96% | |
| | Morphology | 95% | |
| | Syntax | 72% | |
| | Lexicon | 93% | |
| | Semantics | 85% | |

[a] Neurological examination according to Trouillas et al. 1997

[b] Language was assessed with the Italian version of Paradis' Bilingual Aphasia Test (1987). RG performed significantly below the norm on the following subtests: syntactic comprehension, antonyms, mental arithmetic, sentence construction, listening comprehension, dictation of sentences, reading comprehension of sentences. His spontaneous speech mainly showed morphosyntactic errors of agreement between subject and verb (and there is the ambulance which take him to hospital) and between article and noun (the – singular; nurses – plural)

which require smooth handling of complex material, whether of a visuospatial or linguistic nature, although visuospatial information seems harder to process.

In conclusion, the detected deficits are in line with those of the cerebellar cognitive-affective syndrome observed by Schmahmann and Sherman (1998). His evolution over time is remarkable. He started from an extremely severe motor, cognitive, and relational picture as observed during first 7 years of life, to the present situation characterized by a symptomatology composed of mild deficits. A hypothesis could be the existence of conscious learning compensatory strategies (based on declarative memory) more closely linked to the functions of the cerebral cortex. In other words, the cerebral cortex in our patient may have progressively compensated for the functions normally controlled by the cerebellum (Ullman 1997). A similar mechanism (recovery due to the involvement of cortical structures) was hypothesized to interpret the transient nature of some cognitive and linguistic deficits observed in adult patients with acquired lesions of the cerebellum (Molinari et al. 1997). In contrast, recovery of acquired motor and visuospatial deficits is much more reduced (Botez et al. 1989). Although an increasing number of studies have disconfirmed that the adult brain is "hard-wired," knowledge of brain plasticity and possible recovery and compensatory mechanisms elicited by an acquired or congenital brain lesion is still scanty (Robertson 2000). Therefore, the mild motor deficits found in the subject probably confirm the limitations of cerebrocortical recovery strategies. Recovery of his cognitive and relational skills may also be the result of the many rehabilitation trainings he received and the situations to which he was exposed. So this clinical case seems to indicate that, as any other human being during life continues to extend his knowledge, also a subject with brain damage can use his learning skills to compensate for his deficits. This finding may have relevant implications for rehabilitation (Robertson and Murre 1999).

## Conclusions

From the review of the literature 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 disorders of affect (Leiner et al. 1991; Fiez, et al. 1992; Schmahmann 1997, 2010; Schmahmann and Sherman 1998; Fabbro 2000; Gordon 2007; Beaton and Mariën 2010; Murdoch 2010). This picture generally overlaps with the symptomatological profile of CCAS (Schmahmann and Sherman 1998). Severity and range of motor, cognitive, and psychiatric impairments appears to be correlated with earliness, localization, and extent of the agenesis of cerebellum (Chedda et al. 2002). Patients with congenital malformations present indeed 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, presenting either acquired (Levisohn 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) show the more severe clinical picture. In particular, severe pervasive

impairments in social and communication skills (autism or autistic-like behavior), in behavior modulation (self-injury and aggressiveness), and markedly delay in language acquisition, especially in language comprehension have been described by many authors (Gilbert and Coleman 1992; Schmahmann 1991; Kim 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). These studies suggested that vermis (in particular posteroinferior 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 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). Actually, the corrected terminology should be "near total absence of 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 flocculi. Therefore, neuropsychological functioning in this case 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, in particular, visuospatial 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, consequently it is 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; Zettin, et al. 1997; Silveri, et al. 1998; Mariën et al. 2001; Fabbro 2000; Scott et al. 2001; Fabbro et al. 2004; Tavano et al. 2007b, c). Consequently, the neuropsychological and affective disorders in patients with cerebellar pathologies are likely to be a consequence of malfunctioning of a network of complex connections (Schmahmann 2010).

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.

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

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

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