Disorders of cognitive and affective development in cerebellar malformations

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Acquired cerebellar lesions in adults and children can lead to the development of a complex behavioural pattern termed 'Cerebellar Cognitive Affective Syndrome' (Schmahmann and Sherman, Brain, 1998; 121: 561–79), which is characterized by reduced cognitive efficiency associated with specific neuropsychological deficits (executive and visuospatial disorders), expressive language disorders (mild agrammatism and anomia) and affective disorders with blunting of affect. It is not known whether a symptomatological picture such as this can also be found in congenital cerebellar malformations. We studied the behavioural developmental profile of 27 patients including children and adults with congenital malformations confined to the cerebellum, the largest studied sample to date. Extensive clinical and neuropsychological investigations highlight the presence of a wide range of disorders supporting the important role played by the cerebellum in the acquisition of higher-order cognitive and affective skills. The type and extent of cerebral reorganization processes in the presence of malformative lesions are difficult to predict and may possibly account for the variability of clinical phenotypes. It is, therefore, more difficult to identify a syndromic picture defined as exactly as is the case with acquired lesions. However, the pattern of deficits that we document is in remarkable agreement with the general profile of the Cerebellar Cognitive Affective Syndrome. Malformations affecting the cerebellar vermis induce affective and social disorders and evolve towards more unfavourable pictures often associated with an autistic symptomatology. Malformations of cerebellar hemispheres are more frequently associated with selective neuropsychological deficits involving mainly executive functions and visuospatial and linguistic abilities. Motor deficits are generally less severe, and tend to improve slowly and progressively, in some cases reaching almost complete functionality. Finally, the overall favourable evolution with an onset of skills in advanced age in a consistent subset of subjects suggests that individual follow-ups should be performed in order to monitor the quality and stability of impairments and acquired abilities over time.

Keywords: cerebellar malformation; cognition; affect; neurodevelopment; autism

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; CCAS = Cerebellar Cognitive Affective Syndrome; PDD = Pervasive Developmental Disorder

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Introduction

Research on cerebellar functions has focused mainly on motor planning and coordination (Dow and Moruzzi, 1958; Ito, 1984). However, over the past 20 years experimental studies in normal populations and clinical investigations have provided substantial evidence pointing to the involvement of the cerebellum in processing higher-order non-motor functions (Petersen *et al.*, 1988, 1989;

Barker *et al.*, 1991; Akshoomoff *et al.*, 1992; Fiez *et al.*, 1992; Kim *et al.*, 1994; Dennis *et al.*, 1996; Herholz *et al.*, 1996; Riva, 1998; Schmahmann and Sherman, 1998; Silveri *et al.*, 1998; Levisohn *et al.*, 2000; Riva and Giorgi, 2000). In particular, acquired cerebellar lesions may induce disorders of executive functions (Grafman *et al.*, 1992; Courchesne *et al.*, 1994; Tanaka *et al.*, 2003), visuospatial abilities (Wallesch and Horn, 1990; Schmahmann and Sherman, 1998;

Fabbro *et al.* 2004), expressive language (Molinari *et al.*, 1997; Silveri *et al.*, 1993; Fabbro *et al.*, 2004), working memory (Desmond *et al.* 1997; Justus *et al.*, 2005; Ravizza *et al.*, 2006) and affective behaviour (Courchesne, 1991; Courchesne *et al.*, 1994; Schmahmann, 2000). These findings suggest that the cerebellum fulfils an important role in monitoring incoming sensory information and providing online adaptation of both motor and non-motor functions to perform contextually relevant behaviours (Bower, 2002; Ito, 2002; Schmahmann, 2004).

From a clinical viewpoint, Schmahmann and Sherman (1998) used the term 'Cerebellar Cognitive Affective Syndrome' (hereafter termed CCAS) to define a specific pattern of neuropsychological, linguistic and emotional disorders in 20 adult patients with acquired cerebellar lesions. The CCAS is characterized by: (1) disorders of executive functions, specifically planning, set-shifting, abstract reasoning, verbal fluency and working memory; (2) impaired spatial cognition often associated to distractibility, perseveration and inattention, lack of visuospatial organization and memory deficits; (3) speech and language disorders such as dysprosodia, mild agrammatism and mild anomia; (4) personality change with blunting of affect or disinhibited or inappropriate behaviour. Schmahmann and Sherman also found evidence for patterns of association between onset, site and extent of lesion and the resulting clinical profile. A more pronounced expression of the affective cognitive syndrome was associated with bilateral or diffuse cerebellar lesions with acute onset. Lesions affecting the posterior cerebellar lobe caused more marked cognitive disorders, while lesions affecting the anterior lobe caused less pronounced disorders. Vermal lesions were responsible for marked affective and relational disorders.

Schmahmann (2004, 2006) provided an integrative theoretical viewpoint for the widely different nature of the neuropsychological disorders which follow acquired cerebellar lesions. The cerebellum would support the automatic tuning-in of motor, cognitive and affective abilities to a level of homeostasis peculiar to each different function. This regulatory action would be enabled by the specific cerebello-cerebral connections with the associative and paralimbic cortices (Leiner *et al.*, 1991; Schmahmann and Pandya, 1997). Hence, the term 'Dysmetria of Thought' used to define the common nature of impairments which follow acquired cerebellar lesions: patients would be unable to tune-in and display apt behaviours in both higher-order cognitive and affective domains (Schmahmann 1997, 2004, 2006).

After Schmahmann and Sherman's study, other clinical pictures consistent with a CCAS diagnosis have been described in the literature (Paulus *et al.*, 2004). In particular, research on children with acquired cerebellar lesions (Levisohn *et al.*, 2000; Riva and Giorgi, 2000) described syndromic patterns which mainly overlapped with the CCAS in adults. Levinsohn *et al.* (2000) studied 19 children treated surgically for cerebellar tumour and found deficits in executive functions, visuospatial abilities,

expressive language abilities and verbal memory as well as the communicative modulation of emotions. With regard to the lesion site, changes in affect regulation, associated to cognitive and linguistic deficits, were linked to extensive vermal damage but no clear laterality effects were found for cerebellar hemispheric lesions. Similar findings were provided by Riva and Giorgi (2000) who studied 26 children who underwent surgical treatment for cerebellar hemisphere or vermal tumour. Vermal lesions, resulting from the excision of medulloblastomas, determined two different outcomes: (1) post-surgical mutism, which later on evolved into speech or language disorders; (2) disturbances of social and communication behaviour, ranging from irritability to autistic symptoms, with lesions involving vermal postero-inferior lobules. Children with a right cerebellar hemispheric tumour (astrocytoma) showed a decline in verbal abilities, which was, however, non-significant, together with a marked impairment in complex aspects of language, such as the mean length of utterance. Children with left cerebellar tumours also showed a decline in non-verbal abilities together with a more marked decrease in executive functions. However, they also presented with a marked impairment in lexical access. The consistency of the clinical profiles of both adults and children with acquired cerebellar lesions suggests that the cerebellum supports the processing of higher-order functions throughout life, although different types of cerebellar contributions may be interplaying at different ages. These and subsequent studies also documented the likelihood that right cerebellar hemispheric lesions would specifically induce language disorders, however transient, and that left cerebellar hemispheric lesions would give rise to executive and visuospatial disturbances (Fabbro, 2000; Mariën *et al.*, 2001; Scott *et al.*, 2001). However, no definite correlation pattern has been documented yet between specific neuropsychological deficits and a cerebellar hemispheric lesion site (Gottwald *et al.*, 2003; Exner *et al.*, 2004; Fabbro *et al.*, 2004; Gottwald *et al.*, 2004; Grill *et al.*, 2004).

An important issue with respect to the CCAS is whether such a complex nosological picture is limited to acquired cerebellar lesions. Steinlin *et al.* (1999) studied 11 patients with pure non-progressive congenital ataxia with or without cerebellar hypoplasia. Patients were administered the Wechsler's Intelligence Scales, as well as additional clinical neuropsychological tests of attention, memory, language, visual perception and frontal functions. Seven displayed a full IQ from 60 to 92, with verbal abilities which were significantly more preserved than non-verbal ones. The remaining four patients obtained a harmonic full IQ between 30 and 49. In the first group, the authors could find marked difficulties in visuospatial and visuoconstructive abilities. Furthermore, although language abilities and selective attention were normal, sustained attention was impaired. Such findings were in partial agreement with Schmahmann and Sherman (1998) with respect to the type of neuropsychological deficits. However, the impact of

different degrees of cerebellar malformations on neuropsychological functions and affect disorders remained an issue which required further investigation. To this end, Chedda *et al.* (2002) studied eight patients (six children and two adults) with cerebellar agenesis: two cases of near-complete agenesis; two cases with marked hypoplasia of one cerebellar hemisphere (one left, one right); two cases lacking both posterior hemispheres. One adult had vermal agenesis, the other showed agenesis of the right posterior cerebellar hemisphere. These studies documented the presence of motor, neuropsychological and behavioural deficits, which are more marked when the extent of the agenesis is wider. The most important neuropsychological deficits affect executive functions (perseveration, disinhibition, and difficulty in abstract reasoning, working memory and verbal fluency) and visuospatial abilities, with disorders of perceptual organization, visuospatial copying and recall. Some children presented with expressive language difficulties (highly marked in two cases), while all cases displayed marked prosodic difficulties. Behavioural disorders included obsessive rituals, and a marked impairment in understanding social cues. The two adults showed episodes of psychotic depression, which was persistent in one case. In conclusion, substantial data from acquired cerebellar lesions and preliminary information from malformative lesions both seem to highlight the stability and consistency of the clinical description provided by the CCAS.

Our study aimed at verifying the consistency of the diagnostic pattern of the CCAS in the largest group of adults and children with congenital cerebellar malformations (diffused or localized) studied to date. It also aimed at verifying the presence of any association between observed deficits and the site or extent of the lesion. Finally, we wanted to document the change over time in the neuropsychological profiles of patients with congenital cerebellar malformations.

Materials and Methods
Subjects
First, 155 patients were selected with congenital cerebellar lesions who had been referred for hospitalization or follow-up to the Department of Neurorehabilitation of the 'Eugenio Medea' Scientific Institute (Bosisio Parini, LC, Italy) in the 2001–2003 time period. Furthermore, the following exclusion criteria were applied in order to isolate the specific contribution of the cerebellum to the development of cognitive and affective functions: (1) radiological picture or medical history consistent with a diagnosis of acquired lesions due to pre-perinatal suffering; (2) progressive cerebellar pathology; (3) metabolic diseases associated with congenital malformation of the cerebellum; (4) malformation affecting other cerebral structures besides the cerebellum; (5) syndromic patterns involving the cerebellum which can be associated to secondary cortical suffering (e.g. Joubert Syndrome, Arnold Chiari Syndrome); (6) epileptic seizures or febrile convulsions or even focal or generalized paroxysmal EEG abnormalities (spikes or spike-wave complexes)

in the patient's clinical history. There remained 27 patients (17.41%), each of which underwent a general and neurological evaluation as well as psychiatric, neuropsychological and neurolinguistic assessments.

Clinical, developmental and neurological evaluations
Developmental milestones—neuromotor, cognitive, linguistic and affective—were recorded. The items of the Griffiths Mental Development Scale (Griffiths, 1996) were used as indicators of development during infancy, preschool and school age. For each patient, both global and domain-specific (motor, cognition, affect and language) mental age scores were obtained and compared with chronological age to define the degree of severity of developmental delay which was measured as the number of standard deviations from the mean. This was done by means of a thorough review of the clinical records of previous hospitalizations. For each case a standard neurological examination was performed. Cerebellar functionality was studied on the basis of the International Cooperative Ataxia Rating Scale (Trouillas *et al.*, 1996).

Neuroradiological investigation
The neuroradiological study was performed on all the patients using 0.5 or 1.5 Tesla MRI equipment, protonic density and T_1-, T_2-weighted spin-echo sequences, through axial and coronal sections, 4 or 5 mm thick. All the MRI scans were reviewed according to the Atlas of Schmahmman and colleagues (Schmahmman *et al.*, 1999) by a neuroradiologist (T.F.) blind to the patients' identity and clinical data. Malformations were classified into one of the following categories: Type I, complete cerebellar agenesis; Type II, vermal agenesis (complete or partial); Type III, hypoplasia involving the vermis and both hemispheres; Type IV, malformations involving only the cerebellar hemispheres (one or both). This classification allowed us to group patients according to simple ontogenetic anatomical criteria, in line with the normal embryogenesis of the cerebellum (distinguishing paleocerebellum from neocerebellum) (Altman *et al.*, 1992).

Neuropsychological and neurolinguistic assessments
The neuropsychological and neurolinguistic assessments consisted of a battery of tests tailored to the patient's age, cognitive level and level of cooperation. All the tests were used in their Italian version and, where possible, Italian reference norms were used.

Intellectual profile
Wechsler Preschool and Primary Scale of Intelligence (WPPSI, Wechsler, 1973); Wechsler Intelligence Scale for Children—Revised (WISC-R, Wechsler, 1986); Wechsler Adult Intelligence Scale—Revised (WAIS-R, Wechsler 1997); Griffiths Mental Developmental Scale—Revised (1996), Stanford-Binet Scale—Revised (Bozzo *et al.*, 1993).

Attention and memory
Wisconsin Card Sorting Test (Heaton *et al.*, 1993); Tower of London Test (Shallice, 1982); Continuous Performance Test (Cornoldi *et al.*, 1996); Wide Range Assessment of Memory and
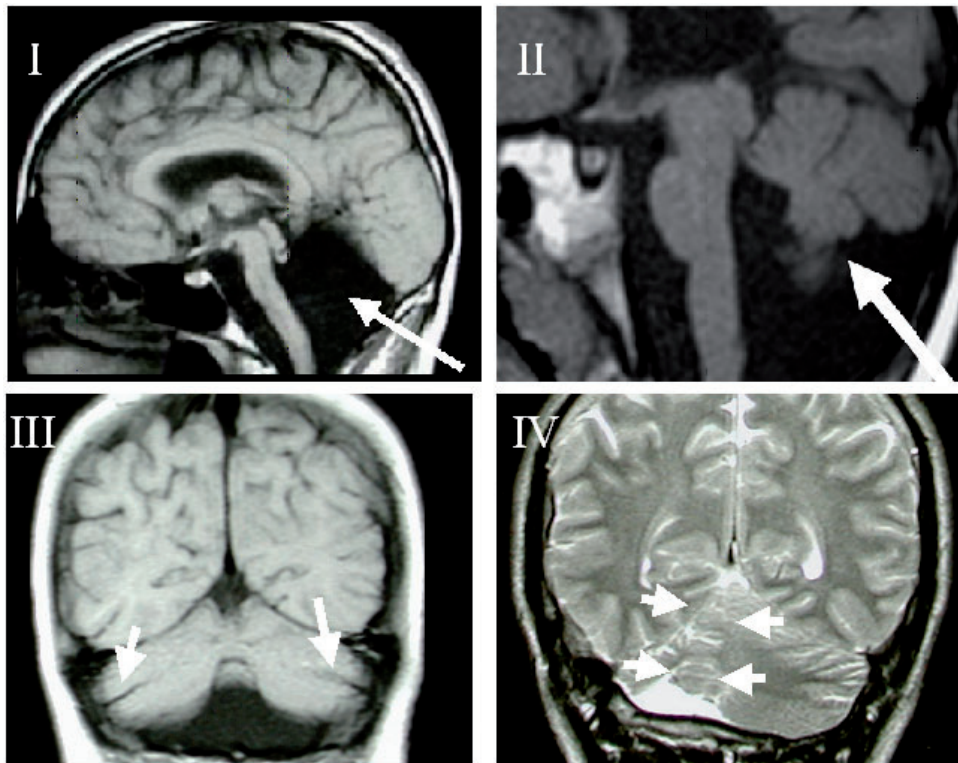
Figure 1 MRI scans of one selected case for each neuroradiological group. Type I = complete cerebellar agenesis; Type II = vermal agenesis (complete or partial); Type III = hypoplasia involving both the vermis and cerebellar hemispheres (see arrows); Type IV = a partially absent right cerebellar hemisphere with a normal vermis slightly tilted to the right (arrows) and normal left cerebellar hemisphere.

Learning (WRAML, Sheslow and Adams, 1990); Rey Complex Figure Test, B (Rey, 1959); Corsi Span (Corsi, 1972); Digit span (Wechsler Memory Scale, Wechsler, 1963). Word span, forward (Spinnler and Tognoni, 1987); Verbal Long-Term Memory Test (Spinnler and Tognoni, 1987); Mirror Star Tracing Task (Sanes *et al.*, 1990).

Perceptual, visuospatial and graphic abilities

Test of Visual-Perceptual Skills (non-motor)—Revised (TVPS, Gardner, 1996); Judgment of Line Orientation (Benton, 1983), Rey Complex Figure Test, A (Rey, 1959); Draw-a-Bicycle Test (Kolb and Whishaw, 1985); Test for Constructive Apraxia (Arrigoni and De Renzi, 1964); Visual Motor Integration Test (VMI, Beery, 2000).

Speech and Language

Children aged 1.06–3.00 (years, months): First Language Test (Axia, 1995).
Children aged 3.00–6.00: Language Assessment Test (Cianchetti and Fancello, 1997).
Children aged 4.00–12.00: Language Assessment Battery (Fabbro, 1999)
Adults: The Bilingual Aphasia Test (Paradis, 1999)

Behavioural and psychiatric evaluation

All the patients received a standard clinical psychiatric assessment. Psychopathological diagnoses were formulated in line with the DSM IV (APA, 1994).

Results

Developmental, clinical and neuropsychological profiles

The 27 selected patients (17 males and 10 females) were divided into four main classes based on neuroradiological classification: one male was diagnosed with complete cerebellar agenesis (Type I); five patients—one female and two males with complete vermal agenesis, and one female and one male with partial vermal agenesis—were included in Type II class; 17 patients, 12 males and 5 females, were diagnosed with diffuse cerebellar hypoplasia affecting both the vermis and the cerebellar hemispheres (Type III); finally, four patients, three females and one male, were diagnosed with agenesis, hypoplasia or dysplasia involving only the cerebellar hemispheres (Type IV). Figure 1 shows the MRI scan of one selected case for each group (see below for one patient's clinical history).

The majority of these patients have been known to us since their first years of life and have been followed-up over the years (mean duration of follow-up: 6.11 years). Currently their ages range from 3.06 years to 34 years (mean age: 11.06 years).

The developmental profiles (Table 1) show a profound retardation in cognition, affect and language for patients from the Type 1 and 2 classes. Type 4 patients generally presented with a record of adequate development.

Table I Developmental milestones according to the Griffiths Mental Development Scale (Griffiths, 1996)

Subject	Gender	Age[a]	Age[b]	Motor	Cognition	Affect	Language
I	M	4.05	34	P	MI	P	MO
2	F	3	12.05	MO	P	P	P
3	M	4	9	P	P	P	A
4	M	5.07	12.01	MO	MO	P	P
5	M	3	8.04	MO	P	P	P
6	F	4.05	6.03	MO	P	P	P
7	M	2	4.09	MO	P	P	A
8	F	3.05	5.06	MO	P	P	P
9	M	3	I0	MI	P	P	P
I0	M	5	I7	MO	P	P	P
II	M	I7	25	MO	MO	MI	MO
I2	F	3	3.06	MO	MI	MI	MI
I3	M	4.05	10.05	MI	MO	MI	MO
I4	M	9	10.05	MI	MO	MO	MO
I5	M	8.02	22.05	MI	MO	MO	MI
I6	F	16.05	2I	MI	MI	MI	MI
I7	M	2.04	5	MI	MI	MI	MI
I8	F	4.I0	19.05	MI	MI	MI	MI
I9	M	2.08	7.0I	MI	MI	MI	MI
20	M	6	10.05	MI	MI	MI	MI
2I	F	II.07	I4	MI	MI	MI	MI
22	M	3.08	5	MI	MI	MI	MI
23	M	2.0I	10.I0	MI	MI	N	MI
24	F	5	6	N	MI	N	MI
25	M	I9	2I	N	N	N	N
26	F	4.05	11.05	MI	N	N	MI
27	F	4.05	11.05	MI	N	N	MI

N = normal; MI = mild retardation (>I SD); MO = moderate retardation (>2 SDs); P = profound retardation (>4 SDs); A = absent.
[a]Age at first evaluation: years, months.
[b]Age at last evaluation: years, months. Continuous lines = main groups; discontinuous lines = subgroups (see text).

However, subjects who have been classified as belonging to the Type 3 class on the basis of a common neuroradiological picture, present with different functional developmental profiles which can be divided into three subgroups: patients 7–10 are similar to patients of Type I and II; patients 11–15 have an outcome of moderate to mild retardation; patients from 16 to 23 showed a mildly impaired to normal developmental trend in cognition, language and affect.

Patients from 2 to 10 present with a diagnosis of Pervasive Developmental Disorder (PDD) (Table 2). Therefore, in these patients there seems to be an association between a marked developmental delay (Table 1) and the actual severe clinical profile. A notable exception is patient 1, who despite a profound developmental delay, was able to acquire almost complete functionality (see the case description below). Patients from 11 to 15 either have no psychiatric problems, or present with disorders characterized by rigidity of thought, aggressive anxiety and an

inability to establish affective bonds. The remaining patients generally present with normal psychiatric profiles; however, two cases present with a diagnosis compatible with that of Attention Deficit Hyperactivity Disorder (ADHD).

The neurological examination shows multiple signs of cerebellar involvement. Ataxia and severe muscular hypotonia are generally present in the most impaired patients. Dysdiadochokinesis (when testable) is the most recurrent sign. Dysarthria is not seen frequently in mildly compromised subjects with the exception of case 21 for whom it is the most relevant sign.

It was possible to obtain an intellectual profile (Table 3) for subjects 1 and 16–27: six patients showed a mild mental retardation, five had a borderline full scale IQ, while two patients achieved a normal intellectual level. These patients seem to have specific drops in abstract reasoning (Arithmetic subtest), tasks requiring praxic as well as working memory efficiency (Coding subtest) and visuoperceptual tasks (Object Assembly subtest). These findings seem to be corroborated by the results of the neuropsychological and neurolinguistic assessments (Table 4), which document the presence of a symptomatological picture compatible with a diagnosis of CCAS.

Specifically, patients who could be tested show consistent impairment in tasks requiring attentional and visuoperceptual skills, while verbal memory and language abilities seem to be more preserved overall.

Follow-up over time shows a progressive improvement, except for patients with a PDD (cases 2–10). In the remaining 18 cases, 13 patients older than 10 years did develop new skills in late infancy. Amongst these, motor abilities were the first to stabilize, while language development continued for far longer than age 8–10 years. Similarly, the specific neuropsychological deficits, while clinically more evident in infancy, were gradually compensated for to varying degrees over time.

Class I: subject with near-total cerebellar agenesis

Class I comprises only one case with complete cerebellar agenesis associated to a mild hypoplasia of the brain stem that is more marked for the pons (Figure 1, type I). This is a rare event (Stewart 1956; Gardner *et al.*, 2001; Titomanlio *et al.*, 2005). Total or near-total cerebellar absence with normal development of the posterior cranial fossa is believed to be the result of an extremely early destruction of the cerebellum which occurred after normal embryological development (Altman *et al.*, 1992; Gardner *et al.* 2001).

Selected case history

Case 1: male, aged 34 years. Despite total cerebellar agenesis, he presents with mild mental retardation, with an harmonic profile (VIQ = 72, PIQ = 67, FIQ = 69) (Table 3). The developmental picture is the most interesting aspect of this case. Although it appeared to be severely compromised during his early years of life, due to a life-long remediation

Table 2 Cerebellar signs at the latest neurological evaluation and psychiatric diagnosis

Subject	Neurological examination					Psychopathological signs	Psychiatric disorders
	HT	DD	A	T	D		
I	+	+	+++	+	+	Rigidity of thought, obsessive traits	N
2	++	nt	++	−	nt	Marked withdrawal, self-injury	PDD
3	++	nt	nw	++	nt	Withdrawal, self-injury	PDD
4	+	nt	++	−	nt	Marked withdrawal	PDD
5	+	nt	+	−	nt	Withdrawal, self-injury	PDD
6	++	nt	++	−	nt	Withdrawal, stereotyped behavior and activities.	PDD
7	+	nt	+	+	nt	Withdrawal, stereotyped behavior and activities	PDD
8	++	nt	++	nt	nt	Symbiotic dimension, autistic traits	PDD
9	+	nt	+	nt	nt	Self-injury and aggressiveness, withdrawal, anxiety	PDD
I0	−	nt	+	+	+	Withdrawal	PDD
II	−	+	+	+	+	Minimal withdrawal	N
I2	++	nt	+++	nt	nt	−	N
I3	+	+	+	−	+	Liability, rigidity, purposelessness	N
I4	+	+	−	−	−	Impairment in reciprocal social interaction with excessive anxiety and worry	AA
I5	−	+	+	+	+	Rigidity of thought and compulsion (repetitive behaviors), excessive anxiety, aggressiveness	OCD[a]
I6	−	+	−	−	−	Minimal depressive traits	N
I7	++	+	−	−	−	−	N
I8	−	+	−	−	−	Anxiety, mild depressive symptoms	N
I9	−	+	−	−	−	Minimal withdrawal	N
20	−	+	−	+	−	Hyperactivity, excessive anxiety	ADHD[a]
2I	−	+	−	−	+++	Anxiety, compulsive traits	N
22	+	+	−	−	−	Anxiety, aggressiveness	N
23	−	+	+	−	+	−	N
24	−	+	−	−	−	Inattention and hyperactivity	ADHD[a]
25	+	+	−	+	−	Mild anxiety	N
26	+	+	−	−	−	Emotional fragility, mild depressive symptoms	N
27	+	+	−	−	−	Emotional fragility mild depressive symptoms	N

HT = Hypotonia, DD = Dysdiadochokinesis, A = Ataxia, T = Intentional tremors, D = Dysarthria; nt = not testable; nw = not walking; +++ = severe deficit; ++ = moderate deficit; + = mild deficit; − = no deficit; PDD = Pervasive Developmental Disorders; AA = Atypical Autism; OCD = Obsessive-Compulsive Disorder; ADHD = Attention Deficit Hyperactivity Disorder; N = no psychiatric disorder. Continous lines = main groups; discontinuous lines = subgroups.
[a]Syndrome-like.

and rehabilitation program this patient achieved a slow and stable progression up to almost adequate levels in each ability (Table 1). A marked hypotonia dating back to the first years of life did not allow him to reach the sitting position until age 2 years. The patient crept without crawling until age 5 years and only achieve walking with an aid at age 10 years, while he achieved unsupported walking at age 22 years. The latest neurological examination only reveals moderate ataxia of gait, mild dysmetria and mild intentional tremor (Table 2). We first saw this patient when he was 4.05 years of age. From a relational point of view he had been described as withdrawn and having autistic traits. He did not look actively for people, and spent much time on his own playing stereotyped and

repetitive games. If looked after, he did not actively avoid contact. Until age 8–10 years he presented with marked emotional fragility and passivity, with ensuing socialization difficulties. During adolescence his interpersonal interaction abilities improved. Today he presents with normal affect without signs of psychopathological behaviour. Overall, his cognitive level is just below the lower limits of the norm and his neuropsychological profile shows selective attention and visuospatial organization deficits. In particular, verbal memory is good, while both spatial and procedural memory are more impaired.

Language development, which was initially markedly impaired, also showed a favourable evolution. The patient

Table 3 Wechsler subtests (Z scores)

WPPSI*		IN	VO	AR	SI	CO	SE		PC	AP	BD	–	GD	MA
WISC-r		IN	VO	AR	SI	CO	DP		PC	CD	BD	PA	OA	MA
WAIS-r°		IN	VO	AR	SI	CO	DP		PC	DS	BD	PA	OA	–
	VIQ							PIQ						
1°	72	−1	−1	**−2.33**	**−2**	**−1.66**	−1.33	67	−1	**−2.33**	**−1.66**	**−2**	**−1.66**	–
16°	63	**−2.66**	−1.33	**−2**	**−2**	**−2**	−0.66	68	−1.33	−1	**−1.66**	−1	**−2.33**	–
17*	86	+0.66	0	**−1.66**	**−1.66**	−0.66	–	50	**−2.66**	**−1.66**	**−2.66**	**−2**	**−2.33**	–
18°	62	**−3**	**−2.33**	**−2**	−1.33	−1.33	**−2.33**	58	**−1.66**	**−3**	**−2.66**	−1.33	**−2.33**	**−2**
19	78	0	−1	**−1.66**	−1	**−2.33**	–	81	−1.33	–	0	−1.33	−1.33	−0.66
20	102	+1.66	+1.33	−1.33	+0.33	−1	−0.33	82	−1.33	**−2.33**	+0.33	−0.33	−0.66	–
21	96	−0.33	−1	−0.66	+0.33	+0.66	−0.33	69	−1	−1.33	**−3**	0	**−2**	**−2.66**
22*	81	−0.33	−1	−1.33	0	**−1.66**	–	73	**−1.66**	−0.33	−0.66	–	**−2.66**	−0.66
23	72	−1.33	−0.66	−1.33	**−2.33**	**−1.66**	**−2.33**	76	−1	−1.33	−0.66	−1.33	−1.33	0
24*	75	−1	**−2**	**−2**	−0.66	−1	–	70	−1	**−2.33**	**−1.66**	**–**	−1.33	−1
25°	107	+1	+1.33	−0.33	0	+0.33	0	100	−0.33	+0.33	+0.66	+1	−1.33	–
26	72	**−2.33**	−1	**−3**	0	−1	**−2**	64	−1.33	**−2.33**	−1	**−2.66**	−1.33	**–**
27	70	−1.33	**−2**	**−3**	−0.66	−1	**−2**	55	**−1.66**	**−3**	−1	**−2.66**	**−2**	**–**

N.B: scores in bold = < −1.5 DS below the mean; − = tests not performed; IN = Information; VO = Vocabulary; AR = Arithmetic; SI = Similarities; CO = Comprehension; SE = Sentences; DP = Digit Span; PC = Picture Completion; AP = Animal Pegs; CD = Coding; DS = Digit Symbol; BD = Block Design; PA = Picture Arrangement; GD = Geometric Design; OA = Object Assembly; MA = Mazes. Continous lines = main groups.

Table 4 Neuropsychological results

N	Global intellectual functioning	Attention	Visuospatial memory	Verbal memory	Visual perceptual skills, motor and visuospatial and graphic skills	Language
1	FIQ: 69	+	−	+	+	+
2	MA: 18 months	nt	nt	nt	nt	+++[a]
3	MA: 12 months	nt	nt	nt	nt	Absent
4	MA: 30 months	nt	nt	nt	nt	+++[a]
5	MA: 30 months	nt	nt	nt	nt	+++[a]
6	MA: 20 months	nt	nt	nt	nt	+++[a]
7	MA: 10 months	nt	nt	nt	nt	Absent
8	MA: 18 months	nt	nt	nt	nt	+++[a]
9	MA: 12 months	nt	nt	nt	nt	++
10	MA: 18 months	nt	nt	nt	nt	++
11	MA: 6years	nt	nt	nt	nt	+
12	MA: 18 months	nt	nt	nt	nt	++
13	MA: 36 months	+	nt	nt	+	+
14	MA: 54 months	nt	nt	nt	nt	+
15	MA: 44 months	nt	nt	nt	nt	+
16	FIQ: 60	+	+	−	+	+
17	FIQ: 64	nt	+	−	++	+
18	FIQ: 56	+	+	−	+	+
19	FIQ: 78	++	++	+	+	+
20	FIQ: 91	+++	+	+	++	+
21	FIQ: 81	++	+	−	+	−
22	FIQ: 74	nt	+	−	+	+
23	FIQ: 71	++	+++	+++	+++	+
24	FIQ: 70	+++	+	+	+	+
25	FIQ: 105	−	−	−	+++	−
26	FIQ: 66	+	+	+	+	+
27	FIQ: 60	+	+	+	+	+

+++ = severe deficit; ++ = moderate deficit; + = mild deficit; − = normal; nt = not testable; FIQ = intelligent quotient based on Wechsler Intelligence Scales according to age, MA = mental age based on Griffiths or Stanford scales, Continuous lines = main groups.
[a]Single-word sentence.

uttered his first words after age 2 years. At age 7 years he uttered single-word sentences. At age 12 years he could build a short and context-related nuclear sentence which enabled him to communicate with his peers. Over time he showed a slow and progressive improvement of linguistic skills and currently his verbal production is functional, although his comprehension of complex sentences is delayed. Verbal expression shows errors in morphosyntax and word choice. His voice is dysphonic (see Tavano *et al.*, 2007, for a detailed description of the subject's language abilities).

Class II: subjects with cerebellar vermal agenesis

This class comprises five patients (mean age 9.07), three males and two females with complete or partial vermal agenesis (absence of the caudal portion).

Developmental milestones and neurological characteristics

Developmental milestones are markedly delayed for all the patients (Table 1) and, contrary to case 1, they do not show any favourable evolution despite the fact that these patients have been on a rehabilitation program for many years (in two cases >7 years). Affective and cognitive abilities are markedly delayed, except for case 4 who presents with a moderate cognitive delay. Linguistic abilities are severely impaired: language is absent in case 3, while the other patients can only utter single-word sentences (Table 4). Motor development is less compromised, even if case 3 shows a severe delay and cases 2, 4, 5 and 6 a moderate delay. It is difficult to interpret the neurological evaluation of these patients as they were poorly cooperative or uncooperative (Table 2). Furthermore, they present with severe hypotonia. Cases 2, 4 and 6 show a markedly ataxic gait and in case 3 gait is almost non-existent. Case 3 also shows severe intentional tremor.

Neuropsychological, neurolinguistic and affective assessment

As these subjects present with severe mental retardation, they could not be tested neuropsychologically and neuro-linguistically. The Griffiths Scale enabled us to establish a mental age ranging from 12 to 30 months (Table 4). These patients all show extremely severe deficits in affect regulation. In particular, their symptomatological picture is characterized by a severe impairment in communication skills, a marked impairment in behaviour modulation and social interaction (self-injury and aggressiveness). A diagnosis of PDD has been made for all the children (Table 2) according to the DSM-IV criteria.

Selected case history

Case 2: female, aged 12.05 years. Normal delivery, with no signs of fetal suffering. The MRI scan shows caudal vermal agenesis and hypoplasia of the cerebellar hemispheres (Figure 1, type II).

The developmental milestones show a marked delay in all areas, except for the motor area. The patient achieved head control at age 5 months, standing at age 15 months and independent walking after the age of 24 months. She currently shows a significant diffuse hypotonia, gait is ataxic and tremor is present. From a relational point of view, she shows autistic traits characterized by withdrawal and a stereotyped pattern of behaviour, interest and activities as well as frequent episodes of aggressiveness and self-injury. Reciprocal social interaction is extremely reduced, she does not perform actions on request, verbal language is extremely reduced and consisting of single-word sentences. She communicates mainly through simple gestures.

Class III: subjects with diffuse cerebellar hypoplasia

Class III comprises 17 patients (mean age: 10.8 years), 12 males and 5 females. These patients present with hypoplasia affecting both the vermis and the cerebellar hemispheres, which are present, yet markedly reduced in volume. This group shows consistent radiological findings but different clinical features. From a clinical viewpoint, patients can be subdivided into three subgroups of decreasing severity: subgroup 1 consisting of cases 7–10 with profound mental retardation and regression behaviours compatible with a diagnosis of PDD; subgroup 2 consisting of cases 11–15 with moderate-severe mental retardation (mental age: ~3 years); subgroup 3 consisting of cases showing mild mental retardation (cases 16–18) or borderline intellectual level (cases 19–23).

Developmental milestones and neurological characteristics

The three subgroups present with different developmental impairments. Patients belonging to subgroup 1 present with a picture that is similar to that of patients with vermal agenesis: a severe impairment of all the developmental milestones, with partially preserved motor skills. The other two subgroups show less severe impairment. Furthermore, the patients from the third subgroup do not show consistent differences in the main functional domains (movement, cognition, language and affect, see Table 1). The neurological examination reveals the presence of a dysdiadochokinesis as a cerebellar impairment in all the patients; patient 21 presents also with marked dysarthria. Muscle hypotonia, tremor and ataxia are found almost exclusively in the most severely impaired cases (Table 2).

Neuropsychological and neurolinguistic assessment

Intellectual, neuropsychological and neurolinguistic assessments involved patients 16–23 (Tables 3 and 4). In all the patients, except for case 19, higher scores were found for

verbal tests than for performance tests. In cases 20 and 21, this difference is significant. A review of the single subtests shows that arithmetic reasoning is the most severely compromised among verbal subtests. However, low scores are frequently observed in visuoperceptual (e.g. Object Assembly, WISC-R) or symbol-digit matching subtests (e.g. Animal Pegs, WPPSI) (Table 3).

The neuropsychological assessment confirms the presence of significant impairments in attention (which are particularly marked in cases 20–23) and visuoperceptual, visuospatial and graphic tasks (Table 4). Memory deficits concern mainly visuospatial memory and, to a lesser extent, verbal memory (Corsi test and Rey Complex Figures Test—Copy and Memory—show mean scores >1 SD below the mean). Last, language is characterized by phonological, lexical and morphosyntactic difficulties in both production and comprehension. No significant prosodic disorders were found. On the sentence repetition task, these patients made errors consisting mainly of omissions of free-standing grammatical morphemes and substitutions of bound morphemes. On the comprehension tasks, these patients were mainly deficient in syntactic comprehension.

Affect

Half of these patients show a psychopathological picture consistent with a psychiatric diagnosis. In particular, a diagnosis of PDD according to DSM-IV criteria could be made for four patients (cases 7–10). The main symptoms include withdrawal, behavioural stereotypies, aggressiveness and self-injury. Case 14 shows a highly marked impairment in reciprocal social interaction (eye-to-eye gaze) and in regulating communication; in addition some repetitive and stereotyped patterns of behaviour are present and suggest a diagnosis compatible with that of Atypical Autism. Case 15 shows rigidity of thought, obsessive traits and compulsive behaviour. In frustrating situations he easily bursts into disruptive acts, sometimes he is aggressive. A diagnosis compatible with that of Obsessive Compulsive Disorder may be made for this subject. Case 20 shows hyperactivity and excessive anxiety with difficult-to-control worrying similar to the pattern described in children with ADHD. In patients 11, 13, 16 and 18, moderate mental retardation is associated to behavioural traits that are not completely adequate, yet they can be more easily ascribed to an intellectual deficit than to a psychopathological picture. Last, three patients with a higher cognitive level (cases 19, 21 and 22) show emotional fragility, poor tolerance to frustration and a mildly depressed mood (Table 2).

Selected case history

Case 21: female, aged 12 years. The MRI scan shows diffuse cerebellar hypoplasia (Figure 1, type III). The patient presents with mild motor delay (sitting was achieved at age 9 months, walking at 16 months) and a mild delay in socio-affective development with eating difficulties since the early
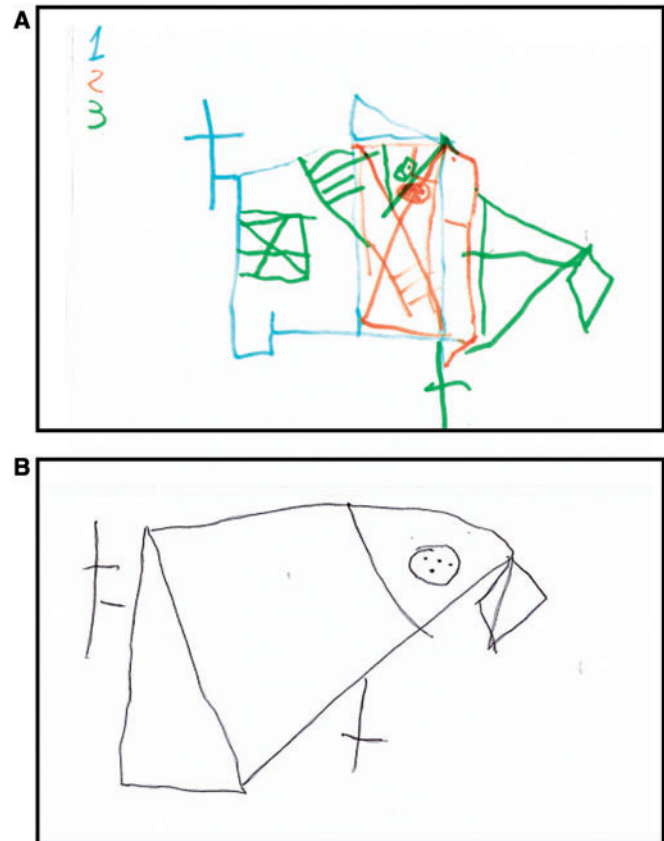
Figure 2 Case 2I, Rey Complex Figure Test. (**A**) copy; (**B**) short-term memory.

years of life and food rejection. She produced her first words at age 24 months and showed articulation disorders at age 9 years. Primary school entry was extremely difficult, especially with regard to learning to read and write. During the first 3 years she was assisted by a support teacher. Later on, learning and oral production improved and today she attends junior high school without the help of a support teacher achieving fairly good results. This patient now shows anxiety, obsessive traits and a depressed mood.

The neuropsychological assessment shows an overall borderline disharmonic intellectual level (FIQ 81) with lower scores on performance tasks (VIQ 96; PIQ 69). The neuropsychological tests show a specific deficit in strategy planning (Wisconsin Card Sorting Test) and praxic constructive abilities (Visual Motor Integration Test). On the 'Draw-a-bicycle' test, this patient achieved a score which correlates with her FIQ (equivalent to a mental age of 10 years) given the high number of details of the bicycle she was able to produce, but the overall representation was very poor because she missed the logical connections between the different elements of the bicycle. Similarly, the Rey Complex Figure Copy Test (Figure 2A) was rather precise and detailed but extremely poor with regard to building strategies, and it revealed an impaired ability to appreciate the organizing structure of the visual task.

On the Rey Complex Figure Memory task (Figure 2B) the overall performance decreased further, being unsupported by an effective operational strategy. The memory deficit seems to be specific for visuospatial planning and sequential tasks (Corsi Test score consistent with a mental age of 8 years), while verbal memory is age-appropriate. Furthermore, the Continuous Performance Test reveals attention problems.

Class IV: agenesis/dysplasia of hemispheres (one or both)

Class IV comprises four patients (mean age 12.05 years), one male and three females with malformations of the cerebellar hemispheres. In particular, cases 24 and 25 show agenesis of the right cerebellar hemisphere, which is virtually non-existent. In cases 26 and 27, two female twins aged 7 years, the malformation affects the cortex of both cerebellar hemispheres (to a greater extent on the right side).

Developmental milestones and neurological characteristics

No specific developmental delay was observed and socio-affective and relational skills were good (Table 1). A mild motor and language delay was found in cases 26 and 27, while case 24 only showed language delay. The neurological evaluation shows a consistent picture for this class: all the patients presented with dysdiadochokinesis and mild hypotonia (cases 25, 26 and 27). Dysarthria and ataxia were absent (Table 2). Case 25 showed a non-familiar left manual preference.

Neuropsychological and neurolinguistic assessment

Patients 26 and 27 show mild mental retardation (FIQ 66, 60, respectively). Patient 25 shows a normal intellectual profile, while patient 24 is borderline. Arithmetic reasoning is the most severely compromised subtest (Table 3). Performance task scores are lower than verbal task scores. The most severely compromised performance tasks require praxic-constructive abilities and attention shifting (Coding, Animal Pegs) and visuospatial and graphic abilities (Block Design, Geometric Design, Object Assembly). The neuropsychological evaluation confirmed the presence of visual perceptual impairment (Rey Complex Figure), which in case 25 was markedly lower than the expected performance and the attention and memory task scores (Table 4). Cases 24, 26 and 27 also showed visuospatial and verbal memory deficits. The Continuous Performance Test revealed significant attention deficits in terms of omissions and the ability to sustain the performance over time. Cases 24, 26 and 27 showed significant semantic and grammatical deficits. Cases 24, 25 and 27 showed deficits in verbal production, specifically omissions of free-standing morphemes and substitutions of bound morphemes.

Affect

These patients did not present with severe behavioural disorders. Case 24 showed cognitive and behavioural symptoms consistent with a diagnosis of ADHD. A diagnosis of psychiatric disorder could not be made in the other cases, yet exaggerated emotional fragility and excessive anxiety were present.

Selected case history

Case 25: male, aged 21 years. The MRI scan showed a marked agenesis of the right cerebellar hemisphere which is almost non-existent (Figure 1, type IV). All the developmental milestones were within the norm. However, as a child he presented with some difficulties in learning to read and write in the first years of elementary school. Later, learning procedures gradually improved and the patient is now attending University with good results. The neurological exam revealed mild diffuse muscle hypotonia, intentional tremor and dysmetria of the right upper limb and dysdiadochokinesis. He also shows excessive anxiety, expressed predominantly through somatic symptoms, for which he is currently under treatment with benzodiazepines.

The overall intellectual level (WAIS-R; FIQ 105; VIQ 107; PIQ 100) was normal and harmonic (Table 3), with a significant drop only in the Object Assembly subtest. The patient also shows planning and problem-solving deficits and visual, graphic and spatial difficulties as evidenced by the Rey Complex Figure Test (Figure 3). In point of fact, on the Rey Figure Copy task the basal organization level was apparently high, even if the organization was impaired by the Style score (intermediate style). The analysis of reconstruction sequences (see colour succession in Figure 3A) shows that this patient takes a casual approach without implementing any strategies and without understanding the relationship between the figure elements. Hence, the impossibility to assimilate the information about organizational principles, making it difficult for the patient to state and generalize concepts. The patient can respond to the physical properties of the stimulus, while he is not able to organize and plan the material, he is oriented to details but shows marked comprehension difficulties concerning the existence of a logical and rational structure. Significant drops were also found on the short-term and long-term Rey Figure Memory task (Figure 3B), where the patient's poor performance is to be ascribed to the above planning and graphic integration difficulties of visuospatial information rather than a specific memory deficit (the patient's performance on a Corsi Test is appropriate). Generally, his verbal performance, both production and comprehension, is normal even if he may occasionally show some grammatical errors (omission of unction words).

Discussion

This work describes the motor, cognitive, linguistic and affective development of children and adults with
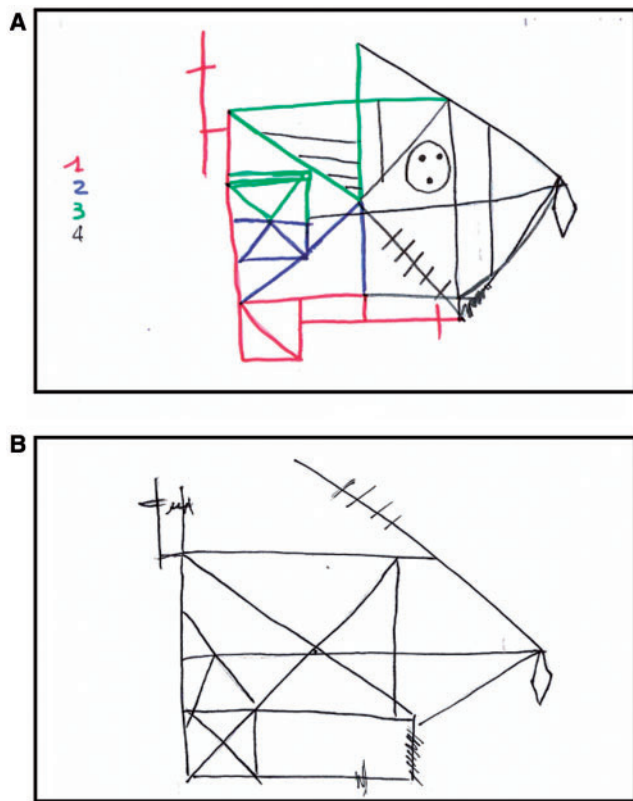
Figure 3 Case 25, Rey Complex Figure Test. (**A**) copy;
(**B**) short-term memory.

congenital malformations of the cerebellum who have been
followed-up for a long period of time (mean follow-up
9 years). The findings of the present work support the
results of previous studies on children and adults with
acquired cerebellar lesions (Schmahmman and Sherman,
1998; Riva and Giorgi, 2000; Levinsohn *et al.*, 2000; Paulus
et al., 2004). Cerebellar malformations bring about a
complex behavioural picture which includes not only
motor disorders but also cognitive disabilities (in particular,
disorders of attentional functions, visuospatial abilities and
spatial and verbal memory), language disabilities (both
expressive and receptive) and disorders of affect. This
picture generally overlaps with the symptomatological
profile of the CCAS (Schmahmman and Sherman, 1998).
Patients with vermal agenesis presented with marked
deficits in motor development, social interaction, intellec-
tual and communicative development. Patients with diffuse
cerebellar hypoplasia may show either a severe syndromic
picture similar to that of patients with vermal agenesis
(patients 7–10) or less severe motor, intellectual, linguistic,
affective and behavioural deficits typical of the CCAS
(patients 11 through 23). An inspection of the intellectual
profiles shows a similar distribution of difficulties for both
the verbal and the performance subscales (Table 3).
However, distinguishing among neuropsychological
domains (Table 4) suggests the existence of an asymmetry

in cognitive outcome, with visuospatial and executive
deficits being greater than language deficits, in line with
Steinlin *et al.* (1999). This is more evident for patients
16–23, but also seems to be valid for patients 24 and 25
belonging to Class IV. Behavioural aspects were relatively
well preserved in both groups.

The retrospective design of our study might have
introduced a bias in patient selection with respect to the
degree of severity, with the result that subjects presenting
with a cerebellar malformation not associated to important
neurological deficits or only associated to minimal clinical
signs might not have been included. In acknowledging this
possibility, we propose that no epidemiological relevance be
attributed to our findings, which should be understood as a
tracing of the main neurodevelopmental trends in different
types of congenital cerebellar malformations.

The developmental delay seems to be more severe—in
particular relational behaviour is more affected—when the
cerebellar malformation selectively affects the phylogeneti-
cally most ancient structures, such as the cerebellar vermis.
In this instance, skill development is severely affected.
In other cases, even in the case of near total absence of the
cerebellum (with partial sparing of the vermis), patients
show a favourable evolution and are capable of acquiring
new skills even at an advanced age, despite the severe initial
delay. At this stage it is therefore not possible to establish
clear correlations between the type of cognitive-affective
deficit and the lesion site/extent. Congenital cerebellar
malformations affect the development of all abilities
(motor, cognitive, affective/relational and linguistic) and
the severity of the resulting deficits is higher than that of all
acquired syndromes in childhood and adulthood. Besides
this, our data do not provide any direct evidence regarding
the issue of functional lateralization and the cerebellum. For
example, we did not find definite and clear-cut pathological
profiles that could tie language abilities to the right
cerebellar hemisphere and visuospatial and/or attention
abilities to the left cerebellar hemisphere, as proposed in the
literature (Mariën *et al.*, 2001). This adds to the absence of
a clear lateralization pattern in former studies of children
and adults with acquired cerebellar lesions (Fabbro 2000,
Riva and Giorgi 2000, Fabbro *et al.*, 2004). Within our
group of patients, the only case pointing to a possible
cerebellar involvement in the organization of hemispheric
specialization is patient 25, who presented with a complete
agenesis of the right cerebellar hemisphere. This patient
presents with non-familiar left manual preference (probably
owing to compensation mechanisms) and a relevant visuo-
spatial deficit, which is similar to that of patients sustain-
ing early left brain hemisphere lesions: in these patients
language development seems to impact on the normal
development of visuospatial abilities (Lidzba *et al.*, 2006).

Cognitive skills

Twenty patients (74%) presented with mental retardation
(FIQ <70), which was specifically mild in six cases

(1, 16–18, 26, 27), moderate-severe in four cases (11, 13–15) and profound mental retardation in ten cases (2–10, and 12). Five patients (19, 21–24) showed a borderline IQ (FIQ 70–85) and two patients (20 and 25) had a normal IQ.

According to our findings, the impact of a congenital cerebellar lesion on cognitive development may lead to three different outcomes:

A. Patients with vermal agenesis and diffuse cerebellar hypoplasia show profound mental retardation and behavioural pictures of withdrawal and social isolation in line with a diagnosis of PDD. The defective development of cognitive and language abilities could be due to the primitive disorder of affect and social interaction (Courchesne, 1991; Courchesne *et al.* 1994a, 1994b; Schmahmann 2000, 2006).

B. A subgroup of patients with diffuse hypoplasia shows extremely rigid and repetitive functioning. The cerebellum seems to have lost its role as 'regulator' and 'mediator' of higher-order functions (Schmahmann, 2004, 2006). It remains to be explained what causes the patients with diffuse cerebellar hypoplasia to split into two dramatically different subgroups, one with a symptomatological picture similar to that caused by vermal agenesis and another with cognitive deficits consistent with the nosological picture of the CCAS (Schmahmann and Sherman 1998, Levisohn *et al.*, 2000; Riva and Giorgi 2000; Chedda *et al.*, 2002). Further genetic and MRI studies will enable us to reach a better understanding of these differences.

C. Patients with lesions confined to the cerebellar hemispheres present a mild cognitive impairment or a borderline IQ, good functioning and context adjustment abilities. Two patients—case 20 belonging to the second subgroup and case 25 belonging to the third subgroup—show a normal cognitive profile. However, these patients also present with lower neuropsychological skills—in particular, visual motor and executive skills—as predicted by the CCAS.

In patients with a normal or slightly delayed cognitive level (belonging to Classes III and IV), visuospatial, visuoconstructive, planning and attention deficits may cause different impairments. This is shown by the Rey Complex Figure test results. The motor performance may be severely impaired (case 21, Figure 2) or in the normal range (case 25, Figure 3). Patients may have difficulty in placing the elements correctly (case 1 and case 21, Figure 2) or may have no difficulty at all (case 25, Figure 3). All patients find it difficult to grasp the structural elements of the figure and task planning, although with different degrees of severity. The most defective patient is case 25 (Figure 3) despite his good graphic skills and ability to perceive the individual elements, while case 1 shows the opposite profile.

Language skills

Language disabilities can be found in almost all the testable patients of our sample and may be extremely variable, ranging from a lack of language abilities (Rekate *et al.*, 1985; Pollack *et al.*, 1995) to morphosyntactic deficits (Silveri *et al.*, 1993; Fabbro 2000, Fabbro *et al.*, 2004, Justus 2004). In two cases (3 and 7), language is completely absent, while in five cases (2, 4–6 and 8) it is limited to single-word utterances. Patients 9–12 present with a marked expressive deficit which however allows for minimal communication. In the remaining cases, language deficits are selective and less severe. It is important to note that language impairments—especially of lexical and morphosyntactic skills—do not only concern production but also comprehension. Hence, the role of the cerebellum in supporting language processing mechanisms underlying the acquisition of both comprehension and production, be they central mechanisms (lexical and morphosyntactic knowledge) or peripheral mechanisms (e.g. verbal working memory) (Desmond *et al.*, 1997; Ravizza *et al.*, 2006; Tavano *et al.*, in press). In line with a picture of PDD, patients with vermal agenesis or hypoplasia show severely impaired language abilities. These findings can be read in the context of the literature, which supports a fundamental role of the vermis in verbal social interaction.

Affect

All the patients with agenesis (partial or complete) confined to the vermis and a subgroup of patients belonging to class III (cases 7–10) present with a severe disorder in social and communicative behaviour, classifiable as PDD according to the DSM-IV criteria. The involvement of the cerebellar vermis (especially its posterior lower portion) in the pathogenesis of the autistic spectrum has been debated for long time and is still under discussion (Courchesne, 1991; Courchesne *et al.*, 1994a, 1994b; Schmahmann 2000, 2006). Our findings seem to support the results of other studies reporting outcomes of surgical vermal ablation in children (Riva and Giorgi, 2000; Aarsen *et al.*, 2004), which describe the onset of autistic-like or hypospontaneous behaviours in their patients. The pathogenetic hypothesis suggests that the cerebellar vermis, together with the structures of the brain stem, the frontal lobes and the limbic system, is involved in associative loops which are responsible for complex social behaviours and, at the same time, the regulation of affect (Schmahmman and Sherman, 1998; Paulus *et al.*, 2004; Docking *et al.*, 2005).

From a psychopathogenetic point of view, the cerebellum, due to its influence on the frontal lobe, seems to be involved in the loops responsible for the inhibition or delay of behavioural responses (Schmahmann, 1997). In our sample, two patients (cases 24 and 20) present with a symptomatological picture consistent with ADHD which underlies the association between underdevelopment of the cerebellar hemispheres or vermis and disorders of attention

and hyperactivity as previously documented by morphometric studies (Berquin *et al.*, 1998).

Finally, the issue may be raised that screening for all pathologies in which a congenital cerebellar malformation is known to be associated to neocortical lesions, does not by itself exclude the presence of subtle disorders of neurodevelopment in other brain areas, at the neocortical and subcortical levels. If present, such lesions might be responsible for the neuropsychological deficits that have been highlighted. This represents a limitation to this study. However, the specificity of the cognitive–affective profile is in line with the concept of a 'CCAS' evidenced in adults with acquired cerebellar lesions (Schmahmman and Sherman, 1998). This, in turn, suggests that undetected subtle lesions, if present, may be responsible, not for the general profile, but for the variability in functional outcome within neuroradiologically defined classes (see Class III).

Evolution

The greatest hindrance to a favourable evolution is the emergence of a PDD. All these patients present with a severe developmental delay, language is severely impaired, and mental retardation is always present. In contrast, all the other patients showed a slow, yet progressive, improvement. The clinical history of patient 1 is eloquent, but all the other patients show the same trend, to a greater or lesser extent. In the literature, except for single case studies, the only work reporting the development of children with non-progressive ataxia from infancy to adult age is of Steinlin *et al.* (1998). The 34 cases described in this study, which partly overlaps with Class III from the present study, were characterized by an improvement in neuromotor symptoms, while the greatest difficulties were caused by the cognitive impairment. Similarly, although part of our patients did show a positive developmental trend, most of them display a moderate to mild mental retardation (only two patients achieved a normal IQ level), thereby preventing the attainment of a full functional compensation.

Conclusions

Our study provides evidence that the cerebellum does not only control motor functions but also the cognitive and affective functions. Its role in supporting learning and the automatic execution of complex behavioural sequences (not only motor sequences) explains why patients with cerebellar agenesis show a delay in all developmental milestones. Though the initial delay may be marked, in some cases it does not preclude the development of other abilities, even at an advanced age (see case 1).

For adults and children with cerebellar malformations and for patients with acquired cerebellar lesions, cognitive and affective deficits are more relevant than motor deficits and give rise to a picture of CCAS. The CCAS observable in patients with congenital malformations seems to be more severe and less specific than that observed in patients with acquired cerebellar lesions. However in patients with cerebellar malformations it is more difficult to establish strict anatomical and functional correlations. The early onset of the malformation and the ensuing neural reorganization make it difficult to establish a neurofunctional profile comparable to that of patients belonging to the same neuroradiological class. It is possible that the neuroradiological investigations carried out in this study did not properly discriminate between patients who later on showed extremely different clinical profiles, as can be observed in patients from Class III. In this case, a diffuse hypoplasia affecting both the vermis and the hemispheres is found both in patients with severe retardation and in patients with limited and specific deficits. Probably, more detailed neuroradiological investigations will enhance our understanding of these cases.

It should however be noted that lesions affecting the phylogenetically most ancient cerebellar structures cause more severe communication disorders; for example, a lesion to the cerebellar vermis causes greater affective relational impairments. The early onset of the disorders and the ensuing severe developmental delay may account for the high number (9 out of 27 in our sample) of patients with a diagnosis of PDD. In the remaining cases, emotional fragility, rigidity and anxiety traits are very frequent. Behavioural fragility—which in some cases may be ascribed to an ADHD-like syndrome—is another frequent finding correlated to the marked impairment of attention skills. When the malformations affect the phylogenetically more recent structures such as the cerebellar hemispheres, specific neuropsychological impairments are noted, as documented in some children and adults with acquired lesions; in particular, visuospatial deficits, problem-solving deficits and language disabilities are seen—especially evident for the morphosyntactic components. Further investigations will enable us to achieve a better understanding of how the functional reorganization process takes place in each single case.

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