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Abnormalities of cerebellar foliation and fissuration: classification, neurogenetics and clinicoradiological correlations

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Abstract Several genes have been found to influence the different cells involved in the processes of foliation and fissuration in the mouse and rat cerebellum. In the light of these new concepts and on the basis of the imaging findings in 42 patients, a classification is proposed for abnormalities of foliation and fissuration. On the basis of recent genetic and experimental evidence on mechanisms which control the origin of the cerebellum, it is suggested that abnormalities of foliation and fissuration form a single group, with a spectrum of severity. Some patients have only abnormal fissuration of the anterior lobe (type 1a) and others additional dysplasia of the anterior and part of the posterior lobe (type 1b). Extension of abnormalities into the hemispheres is often seen in the latter group. A second group has vermian and hemisphere abnormalities (type 2). In addition to the malformation of the anterior lobe of the vermis, three different hemispheric lesions can be seen in this group: cortical dysgenesis, hypertrophy of the cerebellar cortex, and malorientation of the folia. The mild abnormalities (type 1a) can be considered an incidental observation without clinical relevance. The moderate and severe cerebellar anomalies (type 1b and 2) are always associated with cerebellar symptoms and/or signs.

Keywords Cerebellum · Malformations · Magnetic resonance imaging

Introduction

The literature reflects growing interest in developmental malformations of the cerebellar cortex [1, 2, 3, 4, 5]. The main reasons for this are the availability of high-resolution MRI and the interest in involvement of the cerebellum in cognitive processes.

Cerebellar abnormalities were described in the neuropathological literature in the first half of the 20th century [6], but the most detailed imaging reports appeared only after MRI had been introduced. The Chiari malformation, Dandy-Walker complex, Joubert's syndrome, rhombencephalosynapsis and tectocerebellar dysraphia were described in detail in the nineties [7].

Cerebellar cortical developmental abnormalities are common on histology of newborn infants, and may persist to adult life [8]. Cerebellar cortical abnormalities have been associated with Fukuyama congenital muscular dystrophy, Walker-Warburg syndrome and muscle-eye-brain disease but are also reported in the absence of these syndromes too [1, 2, 9]. An association between cerebellar and cerebral cortical developmental abnormalities has recently been reported [5]. Patel and Barkovich presented a classification system for the whole group of cerebellar congenital abnormalities, based on whether they involved the midline, the lateral parts, or both. The purpose of this review is to suggest a classification for abnormalities of cerebellar foliation and fissuration and to study the clinical significance of these lesions.

Anatomy, embryology and neurogenetics

The cerebellum consists of three lobes: anterior, posterior and flocculonodular, separated from each other by the primary and posterolateral fissures, respectively [10]. The flocculonodular lobe develops first, followed by the anterior and posterior. The anterior lobe consists of the vincingulum lingulae and the central, quadrangular (anterior and posterior parts) and superior semilunar lobules. The posterior lobe consists of the inferior semilunar, gracile and biventral lobules and the tonsil [10].

The flocculonodular lobe corresponds to the archicerebellum. The neocerebellum corresponds to the hemispheres except for the flocculi. The paleocerebellum designates the flocculi and the vermis.

The vermis is divided into an anterior lobe (containing the lingula, centralis and culmen), a posterior lobe (containing the declive, folium vermis, tuber vermis, pyramids and uvula) and the nodulus [10]. All lobules are separated from each other by fissures: the precentral fissure between the lingula and the centralis, the preculminate fissure between the centralis and the culmen, the posterior superior fissure between the declive and the folium, the horizontal fissure between the folium and tuber, the prepyramidal fissure between the tuber and the pyramids and the secondary fissure between the pyramids and the uvula. Each lobule can be subdivided into sublobules, which contain a variable number of folia. A folium is a thin transversely-orientated fold of cerebellar parenchyma with a core of white matter, covered by grey matter. The cerebellar white matter, known as the corpus medullare, radiates into the lobules from the centre of the cerebellum (Fig. 1). The branching pattern of primary white-matter tracts is well defined. The lingula, centralis and culmen each have one primary division. In the culmen, there are two secondary anterior and three secondary posterior divisions. In the declive there is one primary and several secondary divisions. The folium, tuber, uvula and nodulus each has one primary division. The pyramids has one secondary or primary division.

Genetic and experimental evidence on the mechanisms which control the origin of the cerebellum and its functional connections is emerging [11, 12]. The cerebellum is now considered as a system in which cells are destined to create the structures. Distinct from the traditional anatomical view of the cerebellum, four transverse zones have been identified as independent from lobulation, each with a unique mixture of Purkinje-cell phenotypes [13, 14]. This was suggested on the basis of patterns of differential gene expression. Several genes, proteins and molecules are involved in the various stages of cerebellar development from the cerebellar primordium to the migration and maintenance of Purkinje cells and the generation and migration of granular cells [12].

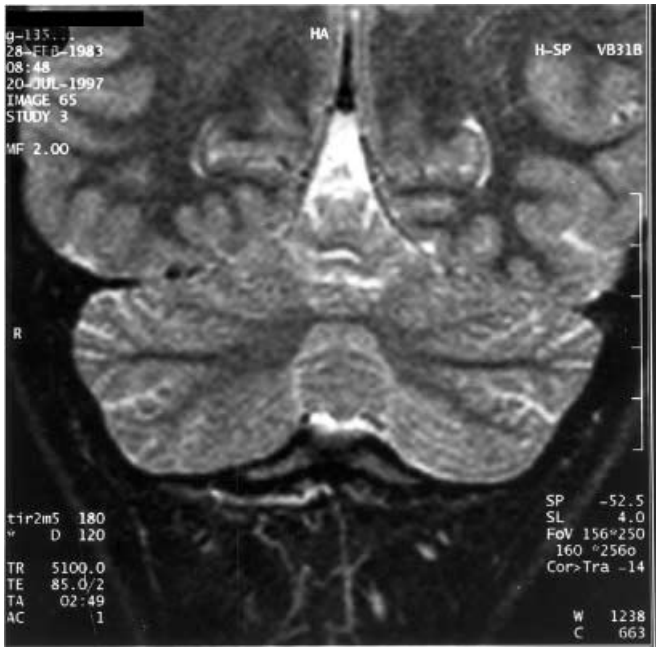

Fig. 1. Coronal T2-weighted image showing normal cerebellar anatomy

Genes which mark the cerebellar territory are expressed in a restricted pattern along the anteroposterior axis of the embryo. The cerebellum arises from the rhombic lip, formed from the alar plate of the rhombencephalon, at around 6 weeks of gestation [7]. The rhombic lip generates precursors of the granular-cell population of the cerebellar cortex and parts of the brain stem. Utsunomiya at al. [15] have shown the rhombic lip to be a single structure with an inverted V-shape, the midportion of which forms the vermis.

A critical region of the embryo, called the ''midbrain-hindbrain'' organiser or isthmus, regulates cerebellar development [16]. The isthmus is a source of hormonal factors, e.g., fibroblast growth factor 8, which regulate proliferation of ventricular cells. Other genes, Gbx 2 homeobox gene and Otx 2, play a role in formation and function of the isthmus. Metencephalic elements are involved in the formation of the hemispheres, and mesencephalic elements in formation of the vermis. Neurogenesis of granular cells gives rise to the formation of the fundamental layers of the cerebellum and to the pattern of foliation.

The vermis is formed by approximately 16 weeks of gestation [17]; development of the cerebellar hemispheres lags behind, by 4–8 weeks. The hemispheric part of the anterior lobe and the simple lobule of the posterior lobe are contiguous with the corresponding structure of the vermis. The vermian and hemispheric parts of the anterior lobe and of the first part of the posterior lobe develop together.

The cerebellar cortex is formed following a complex process consisting of outward and subsequent inward migration. The programmes of gene expression define the granular and Purkinje cells. The Purkinje-cell layer and the deep cerebellar nuclei are formed by migration from the germinal zone along the wall of the fourth ventricle at 8–13 weeks. The Purkinje cells settle beneath the external granular layer, waiting for the inward migration of the granular cells. Mutations in the Reln gene or in components of its signalling pathway lead to cerebellar defects in the mouse [18].

The external granular-cell layer is formed by subpial migration from the lateral portion of the rhombic lips at 10–11 weeks. The molecular and inner granular-cell layers are formed following inward migration of precursor cells from the external granular-cell layer. The external granular-cell layer is present only until the age of about 15 months. A local increase in premigratory cells and an indentation of the Purkinje cells are the trigger for foliation [19].

Individual cell types in the cerebellum have diverse phenotypes and are organised rostrocaudally and mediolaterally in the mouse cerebellum. Pattern formation occurs very early in the cerebellar primordium and continues throughout development [14]. Meningeal cells also play a role in foliation and lamination of the cerebellar cortex; foliation is followed by fissuration.

Generation of granular cells is thought to be instrumental in patterning the tissue and critical in formation of the vermis. The granular cells are the most abundant neurones in the cerebellum and their kinetics are thought to affect the size and foliation patterns of the cerebellar cortex.

Discussion

Compared to malformations of the cerebral cortex, cerebellar cortical developmental malformations have received relatively little attention in the neuroimaging literature. This contrasts with the fact that minor midline cerebellar dysplasias are commonly seen during normal human development [20].

One reason for this is that the cerebellum is a smaller anatomical region and subtle changes are not always shown on routine 5–6 mm axial images. Our group at the University of Leuven found coronal T2-weighted images ideal for studying cerebellar anatomy and abnormalities of foliation and fissuration. In our experience, 3D T1-weighted gradient-echo volume images were of limited use because of the poor signal-to-noise ratio in the cerebellum. It is to be expected that the introduction of phased-array head coils, offering a significantly higher signal-to-noise ratio than the circularly polarised head coil, will improve demonstration of the cerebellum.

At the Annual Meeting of the American Society of Neuroradiology in April 2000, Patel and Barkovich suggested an imaging-based classification of cerebellar malformations, based on a retrospective analysis of 50 patients. Their classification covered all forms of cerebellar abnormality and included 18 patients with a posterior cranial fossa collection, 12 with Joubert's syndrome and eight with rhombencephalosynapsis. A distinction was made between generalised and focal dysplasia. Generalised dysplasia is divided into total, isolated cerebellar or pontocerebellar dysplasia and that associated with congenital muscular dystrophy. The subgroups in focal dysplasia are median (e.g., Joubert's syndrome, rhombencephalosynapsis), lateral and combined lateral and median (e.g. Lhermitte Duclos disease). In this review I consider only a less well-known group of malformations, the abnormalities of cerebellar foliation and fissuration. I shall not discuss entities such as the Dandy-Walker complex, Chiari malformation, Joubert's syndrome and rhombencephalosynapsis. None of our patients had congenital muscular dystrophy, the Walker-Warburg syndrome or muscle-eye-brain disease. It is well known that cerebellar cortical developmental abnormalities, similar to those described here, may occur in these syndromes [9].

In the classification of Patel and Barkovich, abnormalities of foliation and fissuration would be part of the focal dysplasias with median, lateral or combined lateral and median involvement of the cerebellum. I shall use the term "foliation", although the individual folia cannot be recognised on MRI. The lobes, lobules and sublobules can be identified. Although abnormalities of lobulation may be a more correct radiological term, the term foliation is widely used.

The 42 patients with cerebellar vermian and hemisphere abnormalities included individuals with changes only in the vermis, only in the hemisphere(s) or both (Tables 1, 2, 3). We suggest that all these cerebellar abnormalities be considered as one anomaly with variable expression of severity ranging from mild (types 1a, 1b) (Figs. 2, 3) to a severe cerebellar involvement (type 2) (Figs. 4, 5, 6, 7). Many of the patients with abnormal fissuration only (type 1a), underwent MRI, including coronal T2-weighted images and T1-weighted volume imaging as part of investigation for complex partial seizure. The abnormal fissuration may represent an incidental observation in these patients (Table 2).

Abnormal fissuration of the anterior lobe of the vermis can be associated with abnormal foliation (type 1b) (Fig. 3). In the latter, hemispheric extension is frequently seen and the white matter arborisation is less developed (Table 2). This abnormal foliation of the anterior lobe of the vermis can also be associated with dysgenesis (with or without cyst-like inclusions) and/or hyperplasia of the cortex (type 2) (Figs. 4, 5, 7) and/or abnormal orientation of the folia (Fig.6) (Table 3). To

Table 1. Classification of abnormalities of cerebellar foliation and fissuration: diagnostic features

Type	Radiological features
1a	– Malorientation of the fissures in the anterior lobe of the vermis. Cerebellar hemispheric extension of the vermian abnormalities is uncommon.
1b	– Malorientation of the fissures in the anterior lobe of the vermis. – Irregular foliation of the anterior lobe and part of the posterior lobe of the vermis. Cerebellar hemispheric extension of the vermian ab normalities is common. Associated cerebral abnormalities may occasionally be seen.
2	Cerebellar hemispheric abnormalities consisting of one or more of the following: – Cortical dysgenesis (bumpy grey/white matter junction) with or without small included cysts. – Cortical hypertrophy. – Aberrant orientation of the folia. Type 1b changes in the vermis can be seen in more than 60% of the patientsAssociated cerebral abnor malities can be seen in more than 50% of the patients.

describe the bumpy grey-white matter junction, I prefer the term ''dysgenesis'' to ''dysplasia''. The latter is a general term, which usually refers only to a malformation of the neocortex, which exhibits a spectrum of pathological changes. Dysgenesis refers to ''defective development'' without pathological connotation. Small cysts have been described in association with cortical dysgenesis in Fukuyama congenital muscular dystrophy. Their origin is not clear, but they may be related to disordered neuronal migration or represent focal loculations of the subarachnoid space, engulfed by the fusion of disorganised folia (Fig. 4) [9].

Supratentorial developmental abnormalities were seen in seven of 13 patients with a complex cerebellar type 2 abnormality; this proportion is lower than that reported by Soto-Ares et al. [5], who found supratentorial abnormalities in 15 of 17 patients. In contrast with the observations of Soto-Ares et al. [5], all abnormalities in patients with a complex anomaly were bilateral. Soto-Ares et al. 5] also included four patients with the Dandy-Walker complex and Chiari malformation; in their series, vermian dysplasia was always associated with cerebellar hemisphere abnormalities.

Our suggested classification of abnormalities of foliation and fissuration, finds support in the embryology and neurogenetics of the cerebellum. The latter develops in a short time and the processes of migration and foliation occur simultaneously, at least in part, and the migration with an increase of cells represents the trigger for foliation. The two events are closely related. Foliation is followed by fissuration, which explains why abnormal fissuration can be an isolated finding, while abnormalities of foliation are often associated with abnormal fissuration. The external granular cells and Purkinje cell layer may be involved in the process of foliation and both are under genetic control [11]. In rats, aberrant migration and misorientation of the Purkinje cells leads to an abnormal aggregation of granular cells and subsequently to abnormal cerebellar lamination [21]. The migration of Purkinje cells seems to play a key role in the ''cerebellar vermis defect rat'' mutant [21]. A variation of cerebellar foliation pattern of mice is reported to be influenced by loci on chromosome 4 [22]. Vermian and hemisphere dysplasia are closely related. The misorientation of external granular cells leads to aggregation and the consequent abnormal foliation. In the ''rostral cerebellar malformation'' mutant mouse there is a defect in the anterior region of the cerebellum, with missing or abnormal folia. Meningeal cells also play a role in foliation [23]. Differing hormonal sensitivities of the foliation mechanism have been demonstrated in the anterior and posterior potions of the murine cerebellum [24]. It is difficult to estimate at what time during pregnancy the lesions occur, but it is probably in the 4th or 5th month of gestation. Sasaki et al. [25] suggested that abnormal enfolding of a confined

Table 2. Imaging and clinical findings in 29 patients with a type 1 abnormality of cerebellar foliation and fissuration

Type (cases)	Cerebellum	Cerebrum	Clinical features
1a (14)	Abnormal fissuration anterior lobe of vermis (13)	Cortical malformation (2)	Seizures (7) developmental delay (3) learning problems (1) normal (2)
	Abnormal fissuration anterior lobe of vermis with hemispheric extension (1)	Normal	Dyspraxia, cerebellar signs
1b (15)	Abnormal fissuration and foliation anterior lobe of vermis (7)	Cortical malformation (2) with agenesis corpus callosum (1)	Hearing loss, cytomegalovirus infection (1) developmental delay (4) ataxia (1) VIth nerve palsy (2)
	Abnormal fissuration anterior lobe of vermis with hemispheric extension (8)	Hypoplasia corpus callosum (1) cortical malformation (1)	Language and developmental delay (4) cerebellar signs (2) eye movement disorder (3) oculomotor dyspraxia (1)

Table 3. Imaging and clinical findings in 13 patients with a type 2 abnormality of foliation and fissuration

Cerebellum		Cerebrum	Clinical features
Vermis	Hemispheres		
Normal (4)	Cortical dysgenesis with cyst (1)	Malformation of cortex (3)	Developmental delay (2)
Hypoplastic (1)	Cortical dysgenesis with grey matter hypertrophy and abnormal foliation (6)	Malformation of cortex	Seizures
Abnormal fissuration and foliation of the anterior lobe (8)	Grey matter hypertrophy (1)	Agenesis corpus callosum (3) with defective neurulation (1) and/or malformation of cortex (2)	Developmental delay (3) eye movement disorder (1) vestibulo-ocular apraxia (1) headache (1) language problems (1) Leber's congenital amaurosis (1) dysmorphic features (2)

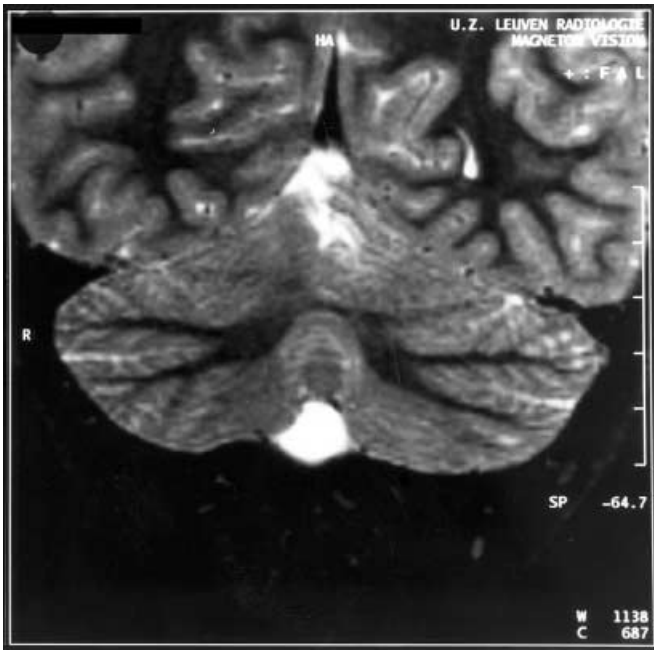

Fig. 2. Coronal T2-weighted image showing abnormal orientation of the fissures of the anterior lobe

area of the hemispheric part of the posterior lobe may have led to a focal abnormality of foliation observed in one hemisphere of two patients [25].

The abnormalities in several patients described by by Soto-Ares et al. [5] would be compatible with our findings and the vertical foliation described in several recent case reports may also be regarded as an abnormality of foliation and fissuration, a more marked type of lesion seen in a spectrum of anomalies [4, 5, 25].

It has been suggested that we consider hypertrophy of the cerebellar cortex, one of the three lesions seen in the complex type 2 cerebellar abnormality, as the Lhermitte-Duclos syndrome [7]. However, the findings in these cases are significantly different from the Lhermitte-Duclos syndrome seen in adults and children, in which high signal is seen on T2-weighted images with some preservation of the cerebellar architecture. We therefore strongly recommend that the term Lhermitte-Duclos syndrome not be used to cover the cerebellar cortical hypertrophy described here. It is probably more likely to resemble the diffuse hemihypertrophy of the cerebellar system reported by Spiegel [26]. In the Spiegel malformation the normal architecture of the cerebellum is preserved, and there is unilateral neuronal hypertrophy in the cortex, white matter, dentate nucleus, pons and cerebellar peduncles.

The patients who form the basis of this review were collected over the past seven years, although most cases seen in the last three years. The use of coronal images and the increased awareness of the sometimes subtle abnormalities are the main reasons for the large series. We would have identified a type 1a abnormality of foliation approximately once a week.

The clinical relevance of the abnormalities seems to correlate with the degree of involvement of the cerebellum. The clinical presentation was highly variable and when there were also supratentorial abnormalities, neurological disturbances were likely to be attributable to these lesions (Tables 2, 3).

The role of the cerebellum as a centre for co-ordination, motor learning and higher cognitive functions is well known. The fact that patients with vermian abnormalities may be asymptomatic supports the suggestion of our group, and others, that the mild changes may represent incidental, clinically irrelevant findings [25]. Walking disability, nystagmus, head- and body turning attacks, mental retardation, developmental delay, hypotonia, lack of interest in the environment and abnormal speech and language development have been described in patients with vermian abnormalities. In a series of 19 patients with ocular-motor apraxia, there was a high prevalence of abnormally small vermis, with a predominant involvement of its inferior portion [27]. In our patients developmental cognitive and motor delay, seizures, language problems, abnormal eye movements and ataxia were the most frequent neurological deficits (Table 2 and 3).

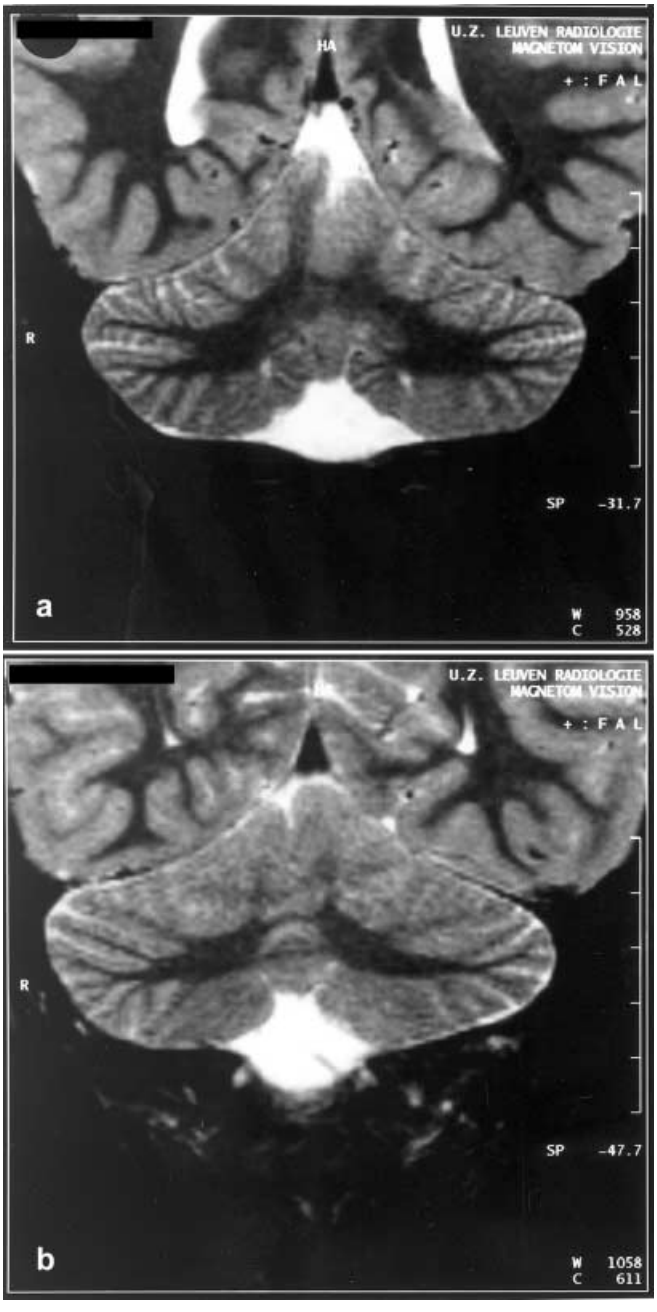

Fig. 3 a, b. Coronal T2-weighted images showing two examples of abnormal fissuration and foliation of the anterior lobe of the vermis, extending to the posterior lobe. Note extension of the abnormalities into the hemispheres and reduced branching of white matter

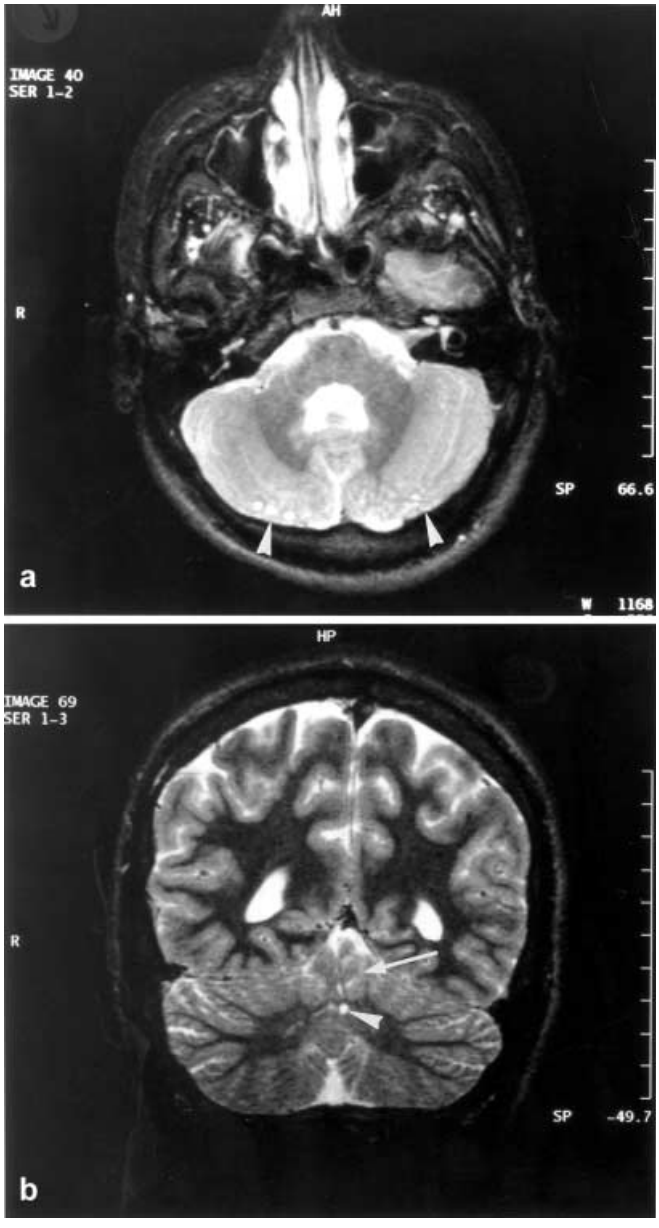

Fig. 4 a, b. Axial and coronal T2-weighted images show cyst-like inclusions in the hemispheres and vermis *(arrowheads)*. Note abnormal foliation of anterior lobe of vermis in **b** *(arrow)*

Thus, vermian abnormalities limited to malorientation of the fissures in the anterior lobe is not an uncommon, but probably represents a minor congenital abnormality that may be considered as an incidental finding without clinical relevance, unless there is extension into the hemispheres. All other cerebellar abnormalities of foliation and fissuration were clinically significant to a variable degree. The dysplastic folia of the anterior lobe can be seen as an isolated finding (type 1b) or in association with dysgenesis and/or hypertrophy of the cortex and/or aberrant folial orientation (type 2). Dysgenesis seems to be a more significant than hypertrophy of the cortex, as it was associated with more severe supratentorial abnormalities and neurology. The overlap between the different types of abnormal foliation and fissuration supports our hypothesis that they may represent one entity with a variable spectrum of severity (Table 1).

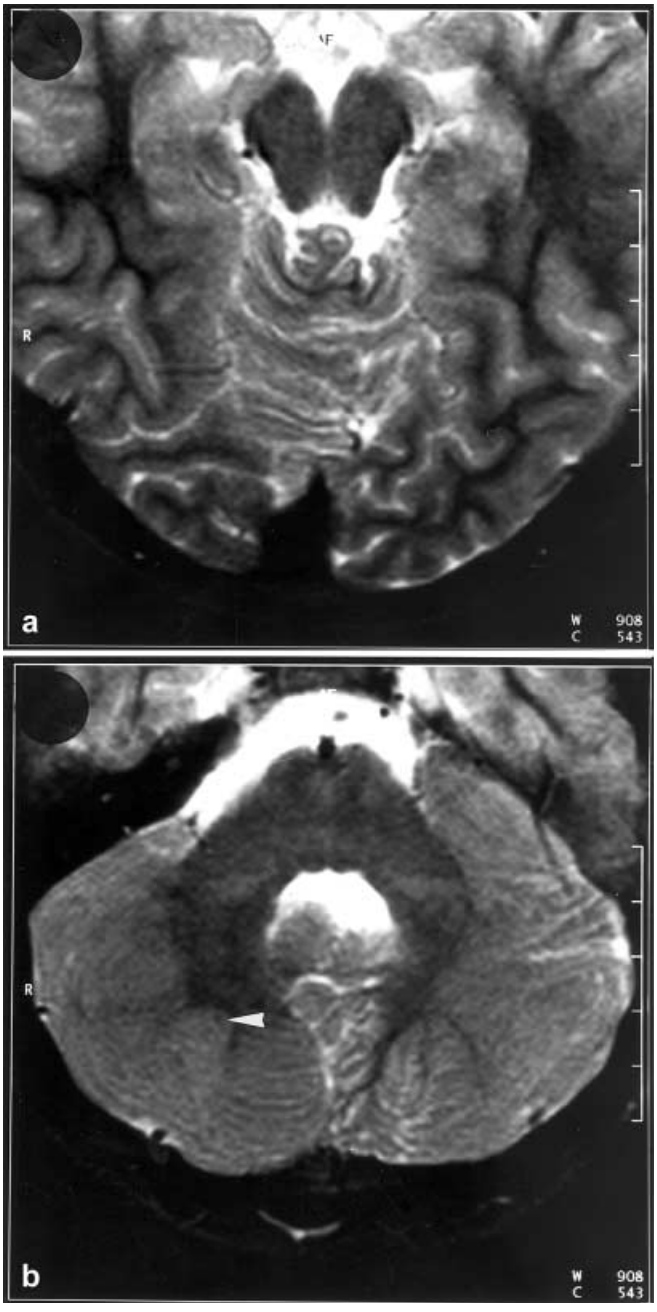

Fig. 5 a, b. Axial T2-weighted images showing abnormal fissuration and foliation **a**, the bumpy grey/white matter interface indicating cortical dysgenesis in **b** *(arrowhead)* and hypertrophy of the cortex on the left

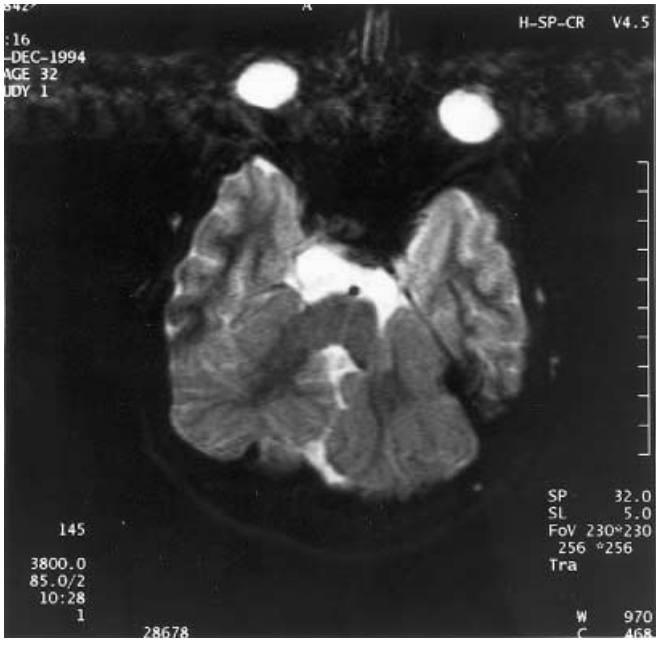

Fig. 6. Axial T2-weighted image showing abnormal orientation of the folia and a hypoplastic inferior vermis

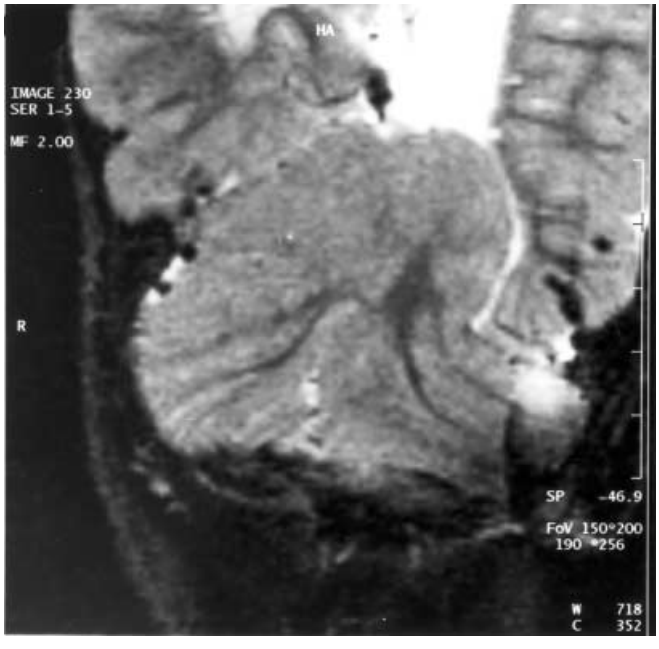

Fig. 7. Coronal T2-weighted image showing hypertrophy of the cerebellum involving the vermis and hemispheres, with cortical thickening.

There is now overwhelming experimental evidence on the complex hierarchy of genetic and cellular interactions involved in the genesis of the cerebellum, with a critical role for the granular and Purkinje cells. Although another type of insult cannot be excluded, it seems likely that a gene expressed in migration and maintenance of the Purkinje cells and/or in the generation and migration of granular cells has mutated and that this disrupts cerebellar migration and foliation.

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