American Journal of Medical Genetics 126A:376–385 (2004)

Research Review

Cerebellum—Small Brain But Large Confusion:
A Review of Selected Cerebellar Malformations and Disruptions

Eugen Boltshauser*

Department of Pediatric Neurology, University Children's Hospital, Zurich, Switzerland

Defining and classifying congenital disorders of the cerebellum can be difficult and confusing. One reason is that some abnormalities called "malformations" are not truly (primary) developmental malformations. This applies to Chiari I "malformations" as well as to Chiari II "malformations." The latter results mainly from a prenatal cerebrospinal fluid (CSF) leak. Also disruptive cerebellar lesions are not uncommon, examples being the "vanishing cerebellum" in myelomeningocele, cerebellar lesions in very low birth weight prematurely born infants, unilateral cerebellar hypoplasia/aplasia, and probably some instances of cerebellar agenesis (CA). The cerebellar hypoplasias consist of a heterogeneous group of inherited and prenatally acquired conditions. The concept of pontocerebellar hypoplasias will need to be expanded beyond the two main types (PCH-1 and PCH-2), and demonstrate that a classification system of cerebellar malformations cannot be based on neuroimaging criteria only. Additional studies are expected to show that this also applies to the molar tooth sign, which was initially described in Joubert syndrome (JS). The JS is the prototype of midhindbrain malformation, but its delineation is still unsolved. JS may well be an overdiagnosed entity; many cases likely not having JS are on record. Rhombencephalosynapsis (RS) has been increasingly diagnosed with the advent of neuroimaging. No familial cases have been observed. Although many affected individuals have variable impairments, RS can be found in children with normal cognitive function. In this review, some of the cerebellar anomalies are briefly discussed.

KEY WORDS: cerebellum; cerebellar agenesis; cerebellar hypoplasia; Chiari I malformation; Chiari II malformation; Joubert syndrome; COACH syndrome; Arima syndrome; vermis hypoplasia; pontocerebellar hypoplasia; molar tooth malformation; rhombencephalosynapsis; cerebellar infarction

INTRODUCTION

In recent years, cerebellar structural abnormalities have gained considerable interest, prompted by several factors:

- The progress with neuroimaging was a fundamental step towards better visualization and increasing recognition of posterior fossa details. Many cerebellar cortical dysplasias [Demaerel, 2002] and other cerebellar anomalies (e.g., rhombencephalosynapsis (RS)) are at present recognizable in vivo.
- It is now accepted that the cerebellum is not only crucial for motor co-ordination, but is also involved in a range of nonmotor (perceptual, linguistic, cognitive, affective) functions [Steinlin et al., 1999]. Therefore, cerebellar malformations are of greater functional consequence than previously thought.
- "New" cerebellar syndromes (e.g., pontocerebellar hypoplasias) have been reported in the last decade.
- Progress has been made in the understanding of brainstem and cerebellar development [Wang and Zoghbi, 2001; Wurst and Bally-Cuif, 2001], but knowledge applicable to clinical relevance of cerebellar malformations is not yet available.

Despite these promising steps, there are still several areas of poor knowledge, confusion, and controversies. The still poorly understood pathogenesis and the difficulties in definitions and delineations result in semantic confusion. Even for the most prevalent malformation, many different terms are used, such as Dandy–Walker malformation, Dandy–Walker syndrome, Dandy–Walker variant, Dandy–Walker continuum, or Dandy–Walker-Blake continuum. In a new classification scheme of cerebellar malformations proposed by Patel and Barkovich [2002], hypoplasias and dysplasias are categorized in a systematic approach. Although an image-based classification is most practical, it has clear limitations: truly developmental malformations are sometimes put in the same category as disruptions (e.g., unilateral hypoplasia), and as there is often considerable phenotypic variability within families and within a single metabolic disorder, patients with identical genetic abnormalities may fall in diverse classes. Furthermore, the delineation of many cerebellar malformations and syndromes is still somehow arbitrary, as long as their pathogenetic mechanism and molecular genetic knowledge is lacking. Therefore, in my opinion, our present lack of knowledge and understanding of etiology and pathogenesis of cerebellar anomalies precludes a complete classification, but with time this will undoubtedly become possible.

Here I will review, guided by personal interest and experience, a selection of cerebellar anomalies, with emphasis on terms frequently used incorrectly, the presumably high susceptibility to cerebellar disruptions, which may mimic true malformations, and the on-going confusion surrounding cerebello-oculo-renal syndromes and the molar tooth malformation.

*Correspondence to: Dr. Eugen Boltshauser, Division of Pediatric Neurology, University Children's Hospital, Steinwiesstrasse 75, 8032 Zurich, Switzerland.
E-mail: eugen.boltshauser@kispi.unizh.ch

Received 30 June 2003; Accepted 9 September 2003
DOI 10.1002/ajmg.a.20662

CHIARI "MALFORMATIONS"

Chiari I Malformation

The so-called Chiari I malformation is defined as an extension of the cerebellar tonsils below the foramen magnum for at least 3–5 mm. The medulla is not caudally displaced and supratentorial anomalies are lacking [Madsen et al., 2002]. Previously, several theories were proposed for the pathogenesis [for review, see Sarnat, 1992]. The most likely and plausible explanation argues that Chiari I malformation is the result of a small posterior fossa, but various processes can lead to caudal tonsillar displacement. There is a correlation between posterior fossa size and the degree of tonsillar ectopia. A high incidence of cranio-vertebral anomalies has been noted in affected patients. A small posterior fossa is a feature in most patients with complex craniosynostosis. Progressive secondary downward displacement of the tonsils can be demonstrated in such situations. The same applies to children affected by skeletal dysplasias resulting in posterior fossa/foramen magnum encroachment [Boltshauser et al., 1996b]. Tonsillar displacement can be observed in particular situations with altered pressure gradients. It is commonly seen in "benign intracranial hypertension" ("pseudotumor cerebri") (Fig. 1) as well as in intracranial hypotension secondary to chronic CSF leak. It is worth mentioning that Chiari I malformation is not a feature in closed spinal dysraphism.

Downward tonsillar displacement is thus usually a secondary (acquired) phenomenon and its designation as "malformation" problematic. The term *tonsillar ectopia*, in relation to its likely pathogenesis, would be a preferable designation.

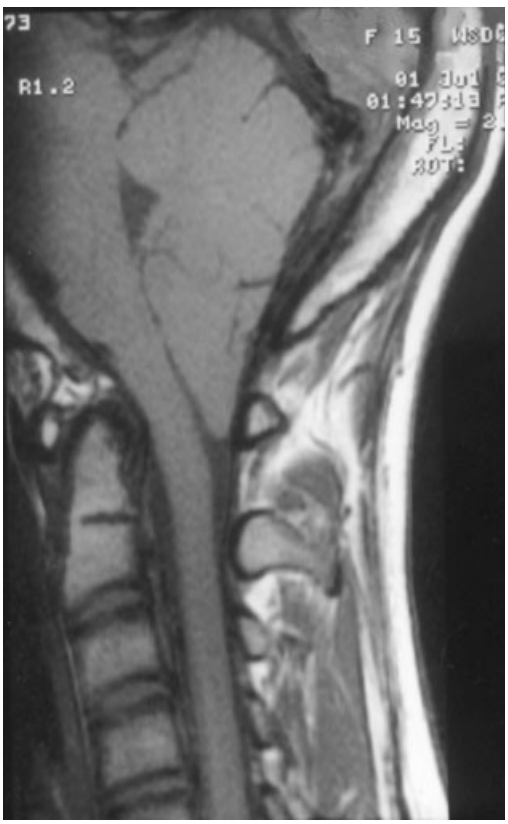

Fig. 1. Sagittal (T2w) MRI. Tonsillar ectopia in a 15-year-old girl with a protracted course of benign intracranial hypertension subsequent to lateral sinus thrombosis.

Symptoms arising from tonsillar ectopia are variable, and it may well be that selection bias is reflected in publications. It seems that the proportion of asymptomatic (incidental) cases increases with the increasing access and use of neuroimaging. The spectrum of associated signs and symptoms includes chronic headache, neck pain, torticollis, lower cranial nerve palsies including nystagmus, ataxia, motor and sensory deficits, scoliosis, sleep-apneas, and unexplained episodes of unconsciousness. Some manifestations result from associated syringohydromyelia. In all patients with tonsillar ectopia, spinal MRI for the assessment of concurrent syringohydromyelia is, therefore, advocated [Barkovich, 2000].

In a recently published retrospective series of 34 children with Chiari I malformation, 21% had scoliosis, several children had sleep apneas or unexplained episodes of unconsciousness, and 26% were asymptomatic [Chartier et al., 2002]. Tonsillar ectopia is usually symmetrical, but asymmetrical instances with unilateral findings do occur [Madsen et al., 2002]. The indication for surgical decompression will not be discussed in this context.

Chiari II Malformation: A "Malformation" Secondary to Prenatal CSF Leak?

The Chiari II malformation is a complex malformation involving the spinal cord and hindbrain, often associated with supratentorial anomalies. All children with Chiari II malformation present at birth with myelomeningocele (MMC). The primary causes of neural tube defects are multifold and still debated, but relevant in practical terms is the significant decrease of MMC by periconceptual supplementation with folic acid [Botto et al., 1999]. Many theories have been proposed to explain the hindbrain abnormalities [for review, see Sarnat, 1992]. The experience with fetal MMC repair [Sutton et al., 1999; Tulipan et al., 1999] has shown that closure of the neural tube defect is able to reduce and even reverse the hindbrain herniation, which, therefore, may be considered to result at least in part from the prenatal CSF leak. As such, Chiari II malformations can be considered to be secondary and thus part of the MMC sequence. The supratentorial anomalies (e.g., corpus callosum dysplasia, neuronal heterotopias) do not seem to be influenced by fetal MMC closure, but this is not sufficiently evident from the literature.

CEREBELLAR DISRUPTIONS

Vanishing Cerebellum in Myelomeningocele

In the MMC, hindbrain herniation through the foramen magnum may result in parenchymal damage. Eventually a grossly reduced or virtually absent cerebellum may be found. This observation was called "vanishing cerebellum in Chiari II malformation" by Sener [1995]. We have seen this phenomenon in three children [Boltshauser et al., 2002]. Interestingly a remarkable asymmetry of tissue damage, affecting mainly one cerebellar hemisphere, was noted. The prevalence of vanishing cerebellum in MMC is not documented. Although, it seems to be infrequent, it is of considerable theoretical interest as a model of cerebellar tissue damage by presumably mechanical factors. In addition, one may argue that the reduced cerebellar volume has an adverse effect on cognitive development, in analogy to the effects of smaller cerebellar volumes in very preterm born infants [Allin et al., 2001].

Cerebellar Lesions in Very Low Birth Weight Premature Infants

Several independent follow-up cohort studies of very low birth weight premature (VLBWP) babies have revealed a significant proportion of unexpected cerebellar defects [for

review, see Boltshauser, 2001; Johnsen et al., 2002]. Most affected children are born before 28 weeks, but it can also be found in neonates born before 32 weeks of gestation, and all have a very low birth weight (less than 1,100 g).

Follow-up MRI reveals mostly symmetric, but also unilateral asymmetric defects of the lower part of the cerebellar hemispheres. In the series reported by Johnsen et al. [2002], the vermis was also affected in half of the children. At least mild atrophy of the pons was seen in all. Cerebral findings (periventricular leukomalacia) were common, but not consistent. While these late imaging findings are increasingly recognized and defined, the timing and nature of the causative events are not. The neonatal courses were not exceptional and there is no positive evidence for a perinatal posterior fossa hemorrhage. On balance, the findings may best be interpreted as infarctions.

Cerebellar tissue loss (irrespective of its origin) seems to be of great functional importance. As reported by Johnsen et al. [2002], VLBWP with cerebellar lesions all had mental retardation. Epilepsy was also a common finding. Even in less expressed cerebellar lesions, a significant association was found between cognitive test scores and cerebellar volume in adolescents who were born very prematurely [Allin et al., 2001].

Unilateral Cerebellar Aplasia/Hypoplasia

The designation *unilateral cerebellar aplasia* (UCA) is problematic. It is a descriptive term (Fig. 2), but lacks pathogenetic explanation. In addition, it may suggest a primary developmental process. We assume that UCA is a prenatally acquired lesion (and, thus, a disruption) and not a true malformation [Boltshauser et al., 1996a]. Similar observations were contributed by Dilhon et al. [2001] and Mancini et al. [2001]. There is obviously a spectrum ranging from complete "aplasia" to subtotal or less pronounced (asymmetric) hypoplasia [e.g., Fig. 4 in Patel and Barkovich, 2002]. Although often symmetric, the obviously acquired cerebellar lesions seen in very prematurely born infants can be unilateral [Johnsen et al., 2002; personal observations]. The nature and timing of the presumed disruptive process is not well documented. In rare instances, the "hemihypoplasia" was detected prenatally [Robins et al., 1998; F. Cowan, personal communication]. As prenatal ultrasound shows no evidence of a cerebellar hemorrhage, I assume that rather ischemic disruptions are causative. If one accepts the possibility of a vascular unilateral disruption responsible for unilateral aplasia, such events could also occur bilaterally (not necessarily simultaneously). This could explain at least some forms of clearly asymmetric cerebellar hypoplasias, and even instances of cerebellar agenesis (CA).

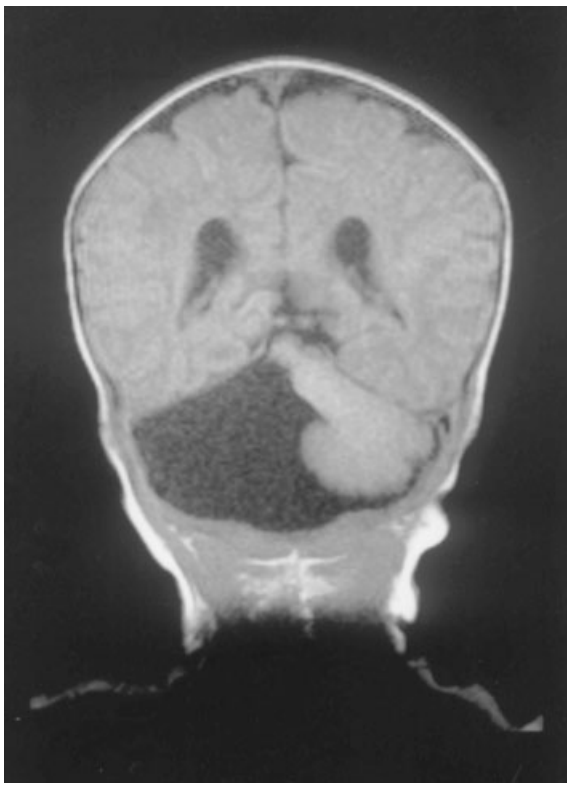

Fig. 2. Coronal (T1w) MRI. Unilateral cerebellar hypoplasia as an incidental finding in a 3-month-old boy with macrocephaly, but no hydrocephaly.

One may argue that fetuses with brain malformations are more susceptible to additional disruption as children with malformations seem to have an increased risk for unilateral cerebellar tissue loss [Boltshauser, 2001]. Having argued for an acquired disruptive process underlying UCA, the classification of "one hemisphere hypoplasia" as a cerebellar malformation in the scheme proposed by Patel and Barkovich [2002] deserves caution.

Cerebellar Agenesis

Despite its extreme rarity, CA has attracted attention as a potential malformation allowing to demonstrate central nervous system plasticity. There is a traditional view that the cerebellum is not necessary for normal motor and cognitive function. An attempt to review the relevant literature here creates confusion, as no clear definition of CA is put forward, because many patients have insufficient clinical or pathological documentation, and many cases with so-called CA have considerable cerebellar tissue present.

Familial cases ("syndromic"). In exceptionally rare instances, CA has been reported in the context of a complex syndrome, associated with presumably X-linked hydrocephalus [Riccardi and Marcus, 1978], and autosomal recessive neonatal diabetes mellitus with microcephaly [Hoveyda et al., 1999]. These affected children died within the first days or weeks.

Sporadic cases. As judged from the literature, all patients with "nonsyndromic" CA have been sporadic observations.

Variability in survival. There is obviously a broad range of life expectancy documented. Some affected individuals died as neonates [Leech et al., 1997; van Coster et al., 1998] or in early childhood [Glickstein, 1994]. On the other hand, Sener and Jinkins [1993] reported a 58-year-old woman.

Variability in cerebellar remnants. Complete (total) CA probably does not occur. In "subtotal" CA at least minute cerebellar tissue corresponding to the anterior quadrangular lobes were documented with MRI [Sener and Jinkins, 1993; Velioglu et al., 1998]. In the majority of reports, considerable amounts of "rudimentary cerebellum" were documented by neuroimaging or post mortem examination [Glickstein, 1994; Leestma and Torres, 2000]. The five patients reported by Gardner et al. [2001] as "near-total absence of the cerebellum" had considerable tissue left, often asymmetric. The inclusion of such patients is problematic.

Clinical findings in CA. Glickstein [1994] concluded his literature review by stating that all cases with complete or near-complete CA had considerable motor deficits. Patients surviving infancy had variable degrees of cerebellar dysfunction (truncal and limb ataxia, dysarthria) as well as cognitive

impairment. The patient with "unappreciated agenesis" who died incidentally at 38 years was unemployed with mental retardation [Leestma and Torres, 2000]. There is only the Sener and Jinkins [1993] 58-year-old, apparently asymptomatic, woman remaining.

Pathogenetic considerations. No familial patients with isolated CA have been published. We have knowledge of a girl with near-complete CA, who has additional cerebral white matter loss (periventricular leukomalacia) although she was born by uneventful delivery (unpublished observation). This is compatible with an acquired event. We also care for identical twins discordant for subtotal CA. Discordance of cerebral malformations in identical twins is well known. This observation also underlies the relevance of epigenetic contributors to the discordance of monozygotic twins. Unilateral cerebellar aplasia can be the result of a unilateral disruptive event—a bilateral disruptive event could be considered as an explanation for CA.

In our view, patients with CA are symptomatic, ranging from extreme (neonatal death) to moderate impairment. If CA is recognized in the prenatal or neonatal period, the course is at present unpredictable. CA may be an acquired anomaly as a result of a disruption. The term CA should be restricted to minute remnants corresponding to the anterior quadrangular lobes.

CEREBELLAR HYPOPLASIAS

Cerebellar hypoplasia denotes reduced cerebellar volume, whilst cerebellar shape is (near) normal (Fig. 3). Pragmatically, a separation in global or generalized hypoplasia (affecting hemispheres and vermis) and selective or focal hypoplasia (affecting either predominantly vermis or hemispheres) can be suggested. In theory the differentiation between hypoplasia and atrophy is straight forward: in hypoplasia the fissures are of normal size compared with the folia, while the fissures are enlarged in atrophy. In practice the distinction is not always as clear and atrophy can be superimposed on hypoplasia (e.g., in Congenital Disorders of Glycosylation). In addition, some patients with nonprogressive cerebellar ataxia presumed to be a static condition have enlarged cerebellar fissures (unpublished observations).

Cerebellar hypoplasia is a heterogeneous condition. As clearly pointed out by Sarnat [1992] and Barth [1993], neocerebellar hypoplasia can be seen in:

- prenatal infections (in particular cytomegalic virus),
- prenatal exposure to teratogens,
- chromosomal aberrations,
- metabolic disorders,
- isolated (genetic) cerebellar hypoplasias,
- complex (genetic) malformations,
- (genetic) migration disorders,
- some types of congenital muscular dystrophies,
- pontocerebellar hypoplasias.

As described above, hypoplasia may result from prenatal vascular disruptions (often asymmetric) and the cerebellar lesions seen in a proportion of very prematurely born infants can perfectly mimic cerebellar hypoplasia, [Johnsen et al., 2002]. In genetically determined cerebellar hypoplasias so far only a few genes have been mapped, one in a large consanguineous Lebanese family at chromosome 9q34 [Delague et al., 2001], another in a genetic isolate (Cayman Island ataxia) [Nystuen et al., 1996].

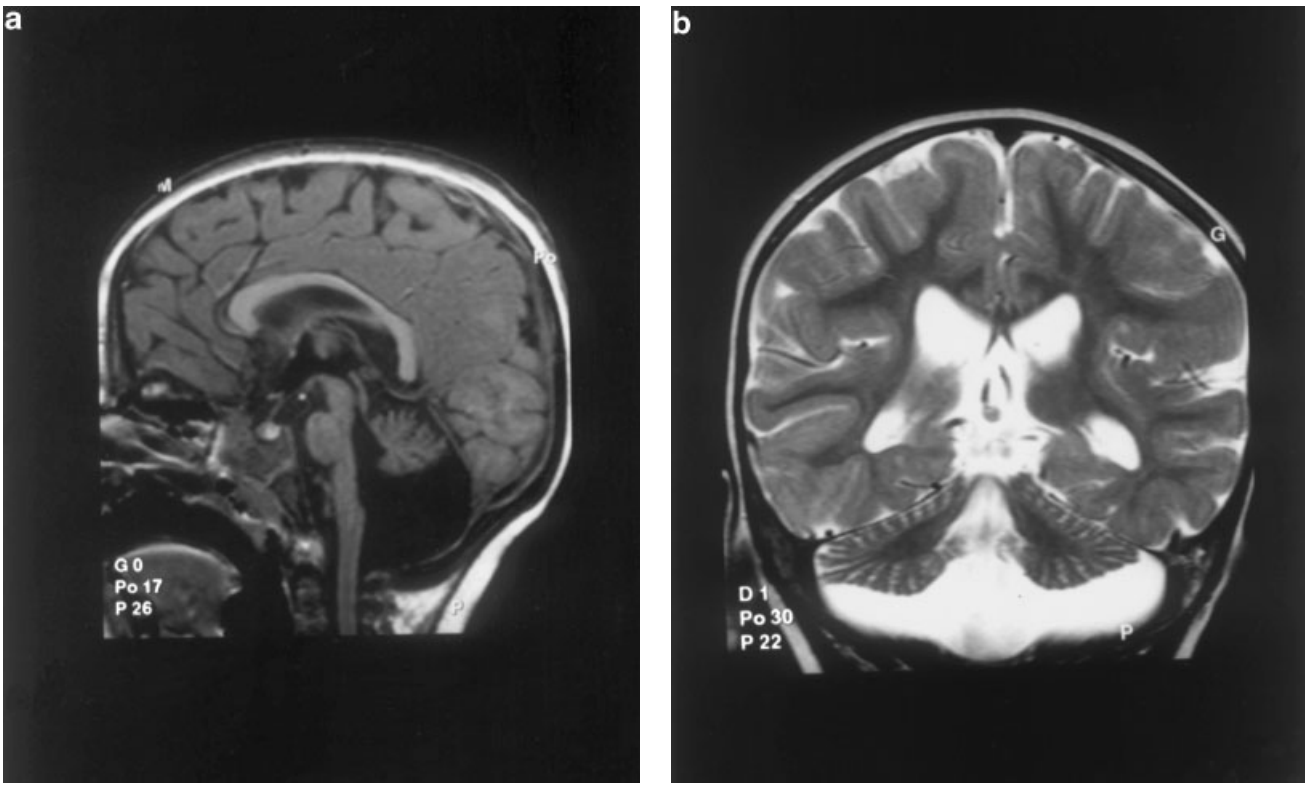

Fig. 3. MRI (**a**: axial T1w, **b**: coronal T2w). Marked cerebellar hypoplasia in a 2-year-old girl with (otherwise unexplained) congenital ataxia and marked motor and cognitive impairment.

In patients with cerebellar hypoplasia, presenting as nonprogressive cerebellar ataxia, the motor deficits tend to prevail in infancy, but language and cognitive impairments dominate in later life, supporting the view that the cerebellum is involved in nonmotor cognitive tasks [Steinlin et al., 1999]. The heterogeneous group of congenital ataxias was reviewed by Steinlin [1998].

The nonrandom combination of the symptoms facial hemangiomas–cerebellar hypoplasia deserves separate mentioning (Fig. 4). Depending on possible additional features, various acronyms have been suggested, the most commonly used being for Posterior fossa malformation, Hemangiomas, Arterial anomalies, Coarctation of the aorta and cardiac defects, and Eye abnormalities (PHACE) [Rossi et al., 2001]. The phenotypic spectrum is broad and the pathogenesis of this neurocutaneus syndrome poorly understood.

PONTOCEREBELLAR HYPOPLASIAS

Barth [1993] is credited for his proposal of the concept of pontocerebellar hypoplasias, representing a group of autosomal recessive neurodegenerative disorders with prenatal onset. He suggested a classification into two main types:

- Type 1 (PCH-1) associated with spinal anterior horn cell degeneration, resulting in polyhydramnios, congenital contractures, microcephaly, gross delay of milestones, peripheral motor system involvement, and resulting in early death.
- Type 2 (PCH-2) without spinal anterior horn involvement, dominated by microcephaly, swallowing impairment, early onset of seizures and extrapyramidal dyskinesia, and lack of development.

Neuropathological examination and neuroimaging demonstrate impressive changes in both entities: pontine hypoplasia, vermis hypoplasia, often with preserved lobulation, and markedly hypoplastic cerebellar hemispheres, of which the thin, wing-like remnants are located below the tentorium. PCH-1 and PCH-2 can not be separated by neuroimaging findings alone (Figs. 5 and 6).

Subsequent publications have confirmed the distinction between the two main types [Barth et al., 1995; Uhl et al., 1998; Muntoni et al., 1999; Coppola et al., 2000; Dilber et al., 2002; Grosso et al., 2002]. The genetic basis of both types is not yet elucidated. Some variation in neuroimaging seems to occur, rendering the diagnosis problematic in some individual patients. In the series published by Muntoni et al. [1999], the autopsy proven Patient 5 had a preserved pontine prominence. The usually preserved vermis lobulation was not recorded in Patient 2 reported by Grosso et al. [2002]. Apparently the spectrum of PCH needs to be expanded. Dilber et al. [2002] observed two siblings with MRI features similar to PCH, but the clinical phenotype was different. They had microcephaly, motor and mental retardation, but not extrapyramidal dyskinesia, and they were ambulant.

The distinction of the different types of PCH towards patients with "subtotal" CA and hypoplastic pons may be problematic. Pontine hypoplasia may also be observed in the context of the previously described lesions seen in very low birth weight prematures.

JOUBERT SYNDROME (JS)

JS: A Prototype of Midhindbrain Malformation

JS was first reported as a form of familial agenesis of the cerebellar vermis in four affected sibs of consanguineous

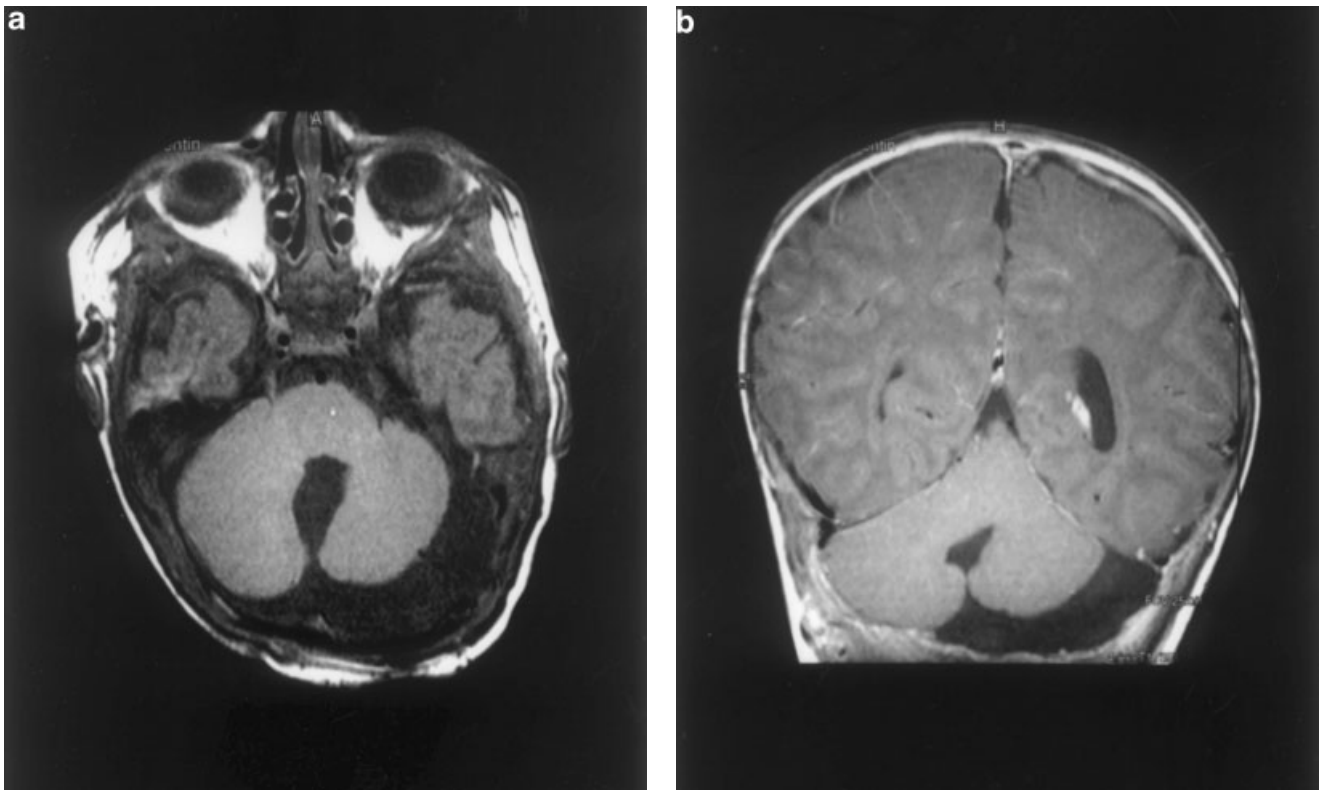

Fig. 4. MRI (**a**: axial T1w, **b**: coronal T1w). Irregular asymmetry of cerebellar hemispheres in a 2-month-old girl with a facial capillary hemangioma. There was no evidence for a leptomeningeal angiomatosis (Sturge–Weber).

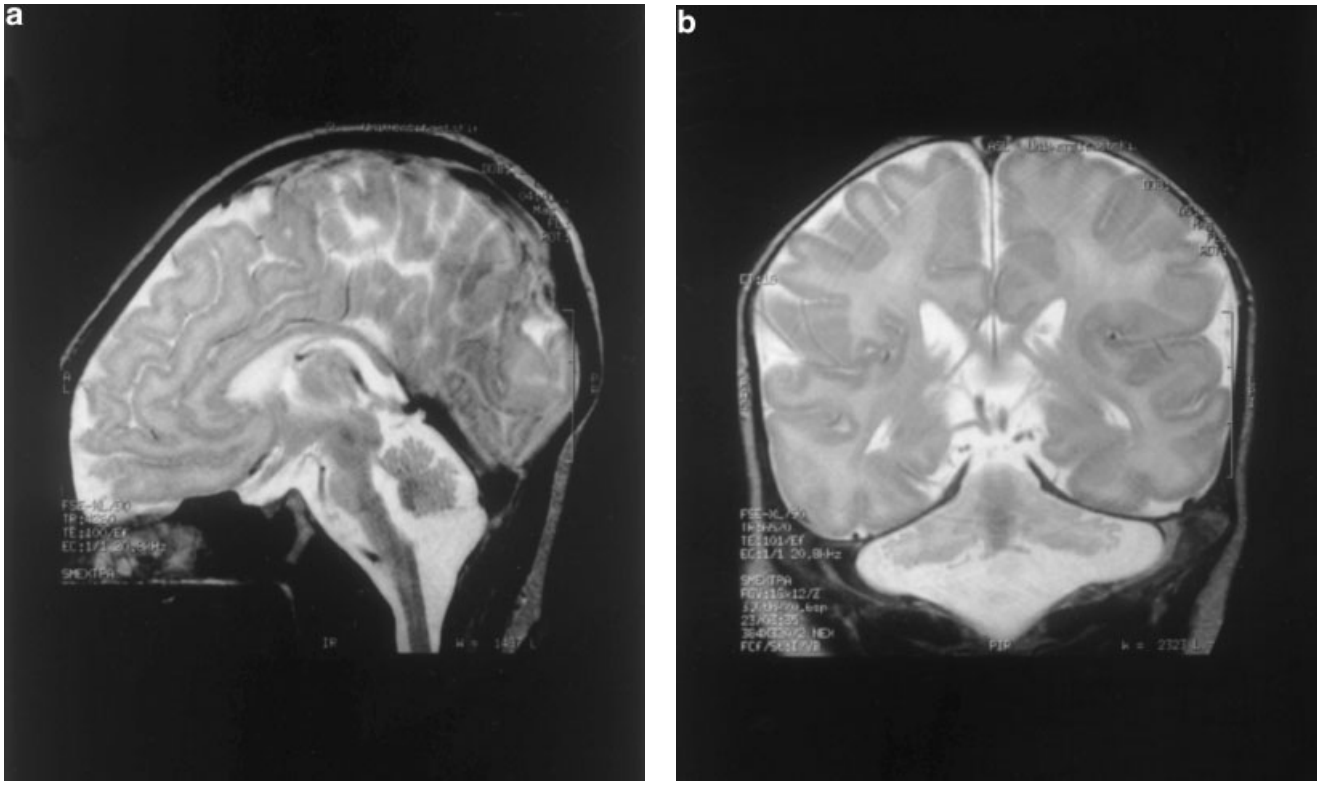

Fig. 5. MRI (**a**: sagittal T2w, **b**: coronal T2w). Pontocerebellar hypoplasia type 2 in a 10-days-old boy with poor spontaneous movement and impaired swallowing, who developed microcephaly later on and had a severely delayed development.

parents [Joubert et al., 1969]. Even this original family forms a good example of phenotypic variability among siblings. Based on the mutual experience of a group of investigators, the following diagnostic criteria have been suggested [Maria et al., 1999a].

Common and consistent abnormalities seen in all patients are:

- muscle hypotonia,
- ataxia,
- developmental delay/cognitive impairment, and
- molar tooth sign (see below).

Frequently associated but not consistent abnormalities are:

- abnormal breathing pattern,
- retinal dystrophy, and
- oculomotor apraxia, upgaze palsy, ptosis.

Rarely observed abnormalities are:

- occipital mengingocele,
- polydactyly,
- short stature,
- scoliosis,
- congenital cataract,
- hydrocephalus,
- hepatic fibrosis, and
- nephronophthisis.

Nephronophthisis has been observed in a minority of patients. It is controversial whether this constellation is part of JS proper, represents a variant, or constitutes a different "overlapping" cerebello-oculo-renal syndrome [Satran et al., 1999]. Epilepsy and microcephaly are not features of JS. Patients tend to have large heads, prominent forehead, high rounded eyebrows, epicanthal folds, occasionally ptosis, upturned nose, and an open mouth with irregular tongue protrusion (in infancy, later rhomboid-triangular shaped mouth) [Maria et al., 1999a]. A range of behavior problems (irritability, episodes of crying, aggressive phases, upset at separation, hypersensitivity to noise) adds to the burden to the families. Follow-up studies confirmed that all affected patients had a variable cognitive impairment [Steinlin et al., 1997].

Maria et al. [1999b] has drawn attention to a characteristic neuroimaging finding—the molar tooth sign (Fig. 7). This was consistently seen in JS patients and, therefore, considered an essential diagnostic feature. It is characterized by:

- in an axial view: deep interpeduncular fossa, thickened superior cerebellar peduncles, batwing shaped forth ventricle, vermis clefting,
- in a coronal view: vermis clefting, rudimentary dysplastic vermis, and
- in a sagittal view: small dysplastic vermis, thin isthmic region.

In view of many familial cases, lack of vertical transmission, and an increased prevalence of consanguineous parents, autosomal recessive inheritance is generally assumed. However, in larger patients series, there is a clear male preponderance, for which no good explanation exists. A gene locus was mapped to 9q34.3 in a large Arab family in 1999 [Saar et al., 1999]. However, in other Arab families and in many American and European families linkage to this locus could be excluded,

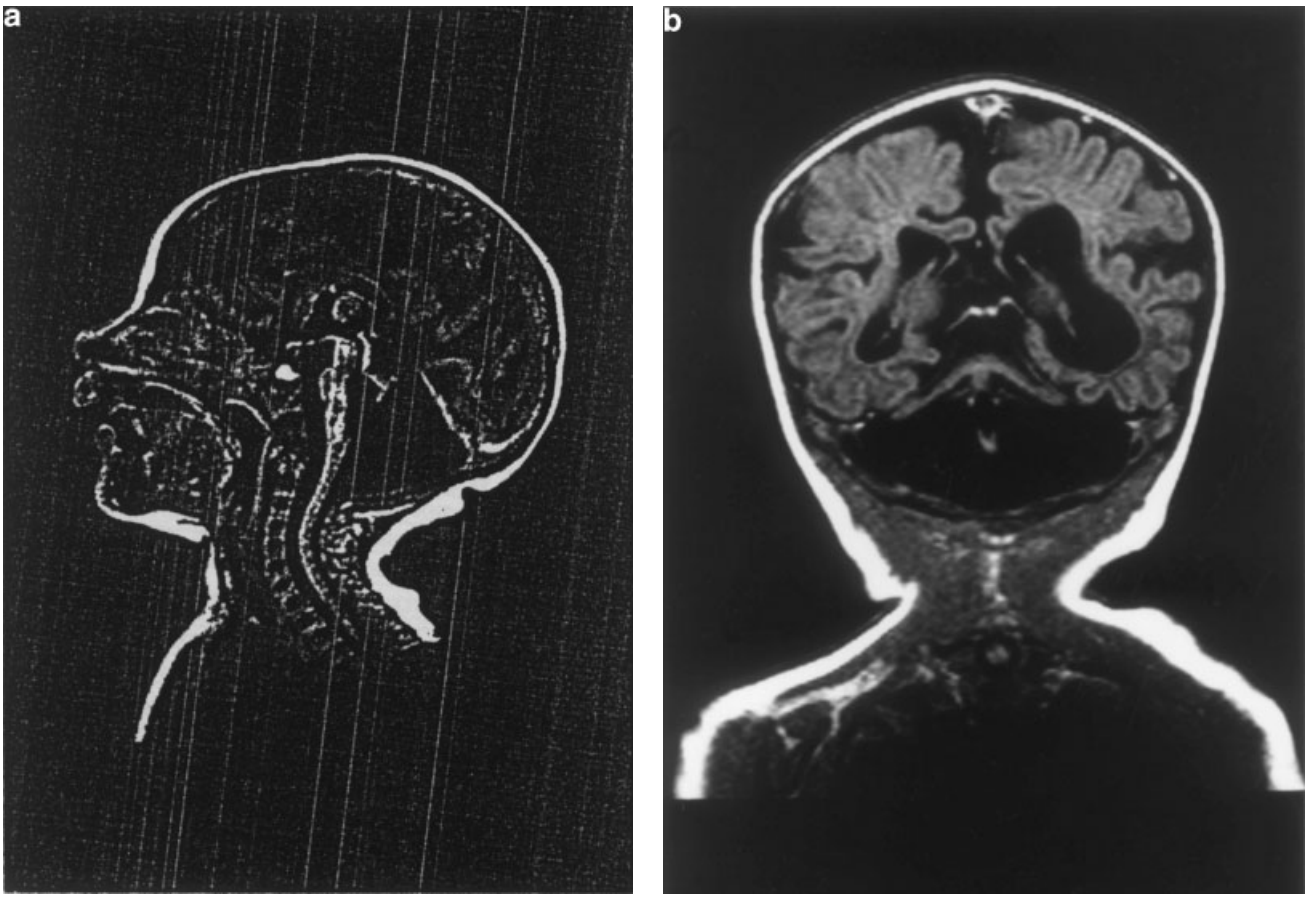

Fig. 6. MRI (**a**: sagittal T1w, **b**: coronal T1w). Marked cerebellar hypoplasia with wing-like hemisphere remnants, pontine hypoplasia, and vermis hypoplasia without preserved lobulation in a 1-week-old girl with microcephaly and absent swallowing. Pontocerebellar hypoplasia type 2 is the most likely diagnosis, but patient is lost to follow-up.

implying genetic heterogeneity. Philip Chance and his coworkers have excluded several candidate genes (e.g., *WNT1*, *FGF8*, *EN1*, *EN2*, *BARHL1*) [Blair et al., 2002].

Judging from personal inquiries over years, it is my experience that JS is overdiagnosed. In a recent letter, attention was drawn to a number of wrongly diagnosed cases [Boltshauser et al., 2002]. In addition, many reports describing patients with Joubert or related syndromes focus on a special aspect such as nephrological symptoms and provide only a vague description of the brain neuroimaging [Keuth et al., 1996; Apostolou et al., 2001]. The molar tooth sign may be quoted, but is not depicted or is even absent in provided illustrations [Coppola et al., 2002]. The delineation of JS from overlapping syndromes is controversial and needs further systematic study. It has (rightfully) been argued that the molar tooth sign (also called molar tooth malformation) is nonspecific and can be observed in other cerebello-oculo-renal-hepatic syndromes [Satran et al., 1999; Ando et al., 2002]. These include, in particular, COACH syndrome, Arima-Dekaban syndrome, Senior-Loken syndrome, and probably other nephronophthisis syndromes, Leber amaurosis, Varadi syndrome, and Meckel-Gruber syndrome. As long as the molecular basis for these disorders is not available, splitting or lumping remains problematic.

A minority of severely affected infants, as judged by lack of any development, have died in the first months of life, without known cause for their demise. Nephronophthisis does influence life expectancy at any age. A number of patients are now in their third and fourth decade. Whether the frequently documented retinal dystrophy is progressive in the long run, needs to be assessed by systematic long-term studies.

RHOMBENCEPHALOSYNAPSIS (RS)

RS is a rare cerebellar malformation, which has recently attracted increasing attention. A review of 23 earlier published cases to which 9 unreported patients were added was recently reported [Toelle et al., 2002]. RS is characterized by dorsal fusion of the cerebellar hemispheres, agenesis or hypogenesis of the vermis, and fusion of the dentate nuclei and superior cerebellar peduncles. A majority of patients has hydrocephalus or ventriculomegaly, and about half has absent septum pellucidum. A spectrum of additional associated abnormalities has been reported, for example, fused thalami, tectum and fornicies, and hypoplastic anterior commisure and temporal lobes.

Clinical findings are quite variable. There is not a clear correlation between neurological findings and neuroimaging. It seems that associated cerebral abnormalities are mainly responsible for the neurological and cognitive impairments. Symptoms of severely affected children include mental retardation, epilepsy, spasticity, and hydrocephalus. On the favorable side of the clinical spectrum, children with isolated RS may have normal cognitive and language function, at least in early school age [Toelle et al., 2002]. A particular, but only occasionally observed, finding is involuntary lateral

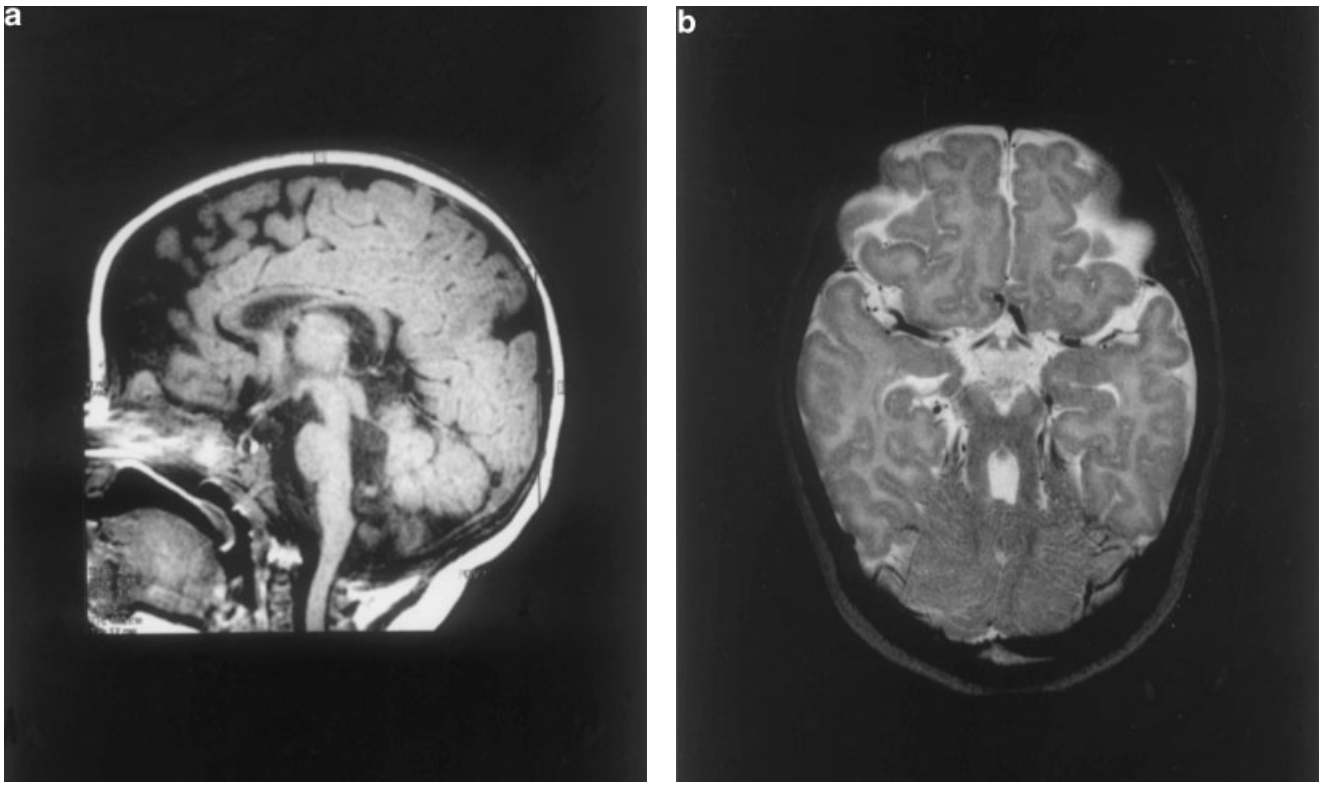

Fig. 7. MRI (**a**: sagittal T1w, **b**: axial T2w). Joubert syndrome (JS) in a 4-month-old boy. The sagittal view illustrates the thin isthmic region, an unusually shaped fourth ventricle as well as vermis dysplasia. The axial view illustrates the molar tooth sign with deep interpeducular fossa and stretched, and thickened superior cerebellar peduncles.

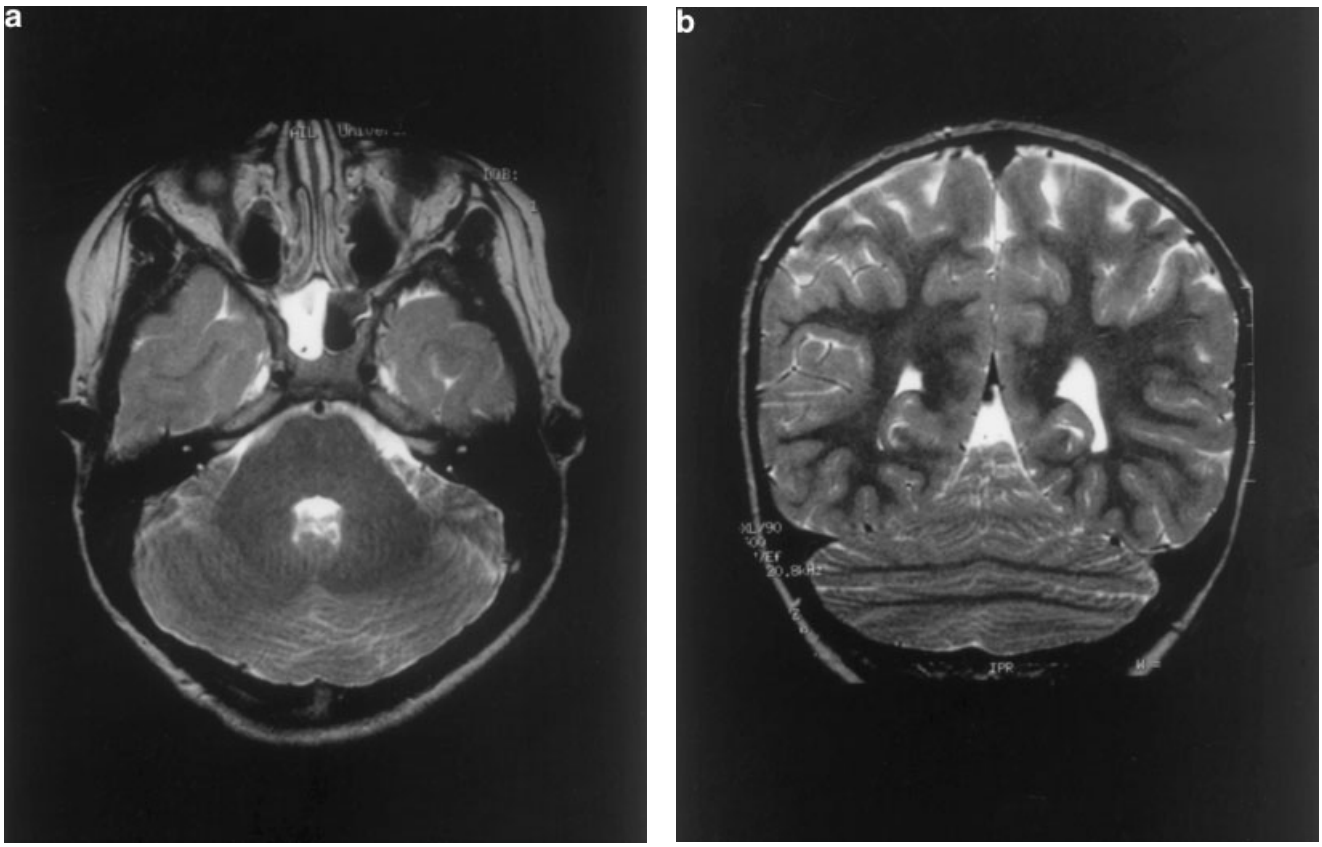

Fig. 8. MRI (**a**: axial T2w, **b**: coronal T2w). Rhombencephalosynapsis in a 9-year-old, normal intelligent girl with truncal ataxia and intermittent lateral head nodding. A: Fusion of the cerebellar hemispheres. B: Horizontal orientation of posterior cerebellar folia without intervening vermis.

movements ("head rolling") [Hottinger-Blanc et al., 2002]. This phenomenon was also present in a recently diagnosed girl who follows a special class for children with above average intelligence (Fig. 8).

A reliable neuroimaging diagnosis is not possible on mid-sagittal views. It is best confirmed on *posterior coronal MRI* demonstrating abnormal horizontal folial orientation. This aspect is not sufficiently evident from *anterior coronal* cuts. A key-hole appearance of the fourth ventricle is an inconsistent finding in the axial plane.

RS results from a disturbed development of the cerebellum at 28–41 days of gestation, and should be considered as a developmental disorder mainly affecting mid-line structures. All cases published until now have been sporadic [Toelle et al., 2002]. Mendelian inheritance seems almost certainly excluded.

RS may be part of the Gomez–Lopez–Hernandez (cerebello-trigeminal-dermal dysplasia) syndrome [Brocks et al., 2000]. The combination of RS and myelomeningocele was previously reported [Leiz et al., 2000]. However, a diagnosis of RS should only be made with great caution in this context, as the posterior fossa is small and cerebellar distortion may mimic the appearance of RS. In a fetus a complex malformation of the cerebral (telencephalosynapsis) and cerebellar hemispheres (RS) with a Dandy–Walker-like posterior fossa cyst was described [Sergi et al., 1997]. This constellation has also been observed by Sener (personal communication).

CONCLUSIONS

Classifying the different congenital cerebellar abnormalities remains difficult. It is expected that at least part of the present confusion and uncertainty will be cleared by progress in the understanding of cerebellar embryology, identification of the complex array of genes involved in brainstem and cerebellar development, insight gained from animal studies, and identification of genes responsible for human cerebellar malformations, such as JS and pontocerebellar hypoplasia. A careful, pattern recognition approach considering clinical, neuroimaging, genetic, and other possible variables is the basis for further delineation of cerebellar anomalies. Pooling of data of the often rare anomalies and evaluation in expert working groups may prove successful.

ACKNOWLEDGMENTS

I am grateful to Dr. E. Martin, Dr. Ch. Rauscher, Dr. J.F. Schneider, Dr. A. Tscharre, and Dr. M. Weissert for sharing case records, neuroimaging findings, and their experience.

REFERENCES

Allin M, Matsumoto H, Santhouse AM, Nosarti C, AlAsady MH, Stewart AL, Rifkin L, Murray RM. 2001. Cognitive and motor function and the size of the cerebellum in adolescents born very pre-term. Brain 124:60–66.

Ando K, Ishikura R, Takada Y, Morikawa T, Nakao N, Ikeda J, Mae H, Tanizawa T. 2002. CNS imaging findings of a case of COACH syndrome. Neuroradiology 44:542.

Apostolou T, Nikolopoulou N, Theodoridis M, Koumoustiotis V, Pavlopoulou E, Chondros D, Billis A. 2001. Late onset of renal disease in nephronophthisis with features of Joubert syndrome type B. Nephrol Dial Transplant 16:2412–2415.

Barkovich AJ. 2000. Pediatric neuroimaging, 3rd edition. Philadelphia: Lippincott Williams & Wilkins. 329 p.

Barth PG. 1993. Pontocerebellar hypoplasias. An overview of a group of inherited neurodegenerative disorders with fetal onset. Brain Dev 15:411–422.

Barth PG, Blennow G, Lenard HG, Begeer JH, van der Kley JM, Hanefeld F, Peters AC, Valk J. 1995. The syndrome of autosomal recessive pontocerebellar hypoplasia, microcephaly, and extrapyramidal dyskinesia (pontocerebellar hypoplasia type 2): Compiled data from 10 pedigrees. Neurology 45:311–317.

Blair JP, Gibson RR, Bennett CL, Chance PF. 2002. Search for genes involved in Joubert syndrome: Evidence that one or more major loci are yet to be identified and exlusion of candidate genes EN1, EN2, FGF8, and BARHL1. Am J Med Genet 107:190–196.

Boltshauser E, Steinlin M, Martin E, Deonna Th. 1996. Unilateral cerebellar aplasia. Neuropediatrics 27:50–53.

Boltshauser E, Schmitt B, Wichmann W, Valavanis A, Sailer H, Yonekawa Y. 1996. Cerebellomedullary compression in recessive craniometaphyseal dysplasia. Neuroradiology 38:193–195.

Boltshauser E. 2001. Cerebellar imaging—An important signpost in paediatric neurology. Child Nerv Syst 17:211–216.

Boltshauser E, Schneider J, Kollias S, Waibel P, Weissert M. 2002. Vanishing cerebellum in myelomeningocele. Eur J Paediatr Neurol 6:109–113.

Boltshauser E. 2002. Joubert syndrome: More than lower cerebellar vermis hypoplasia, less than a complex brain malformation. Am J Med Genet 109:332.

Botto LD, Moore CA, Khoury MJ, Erickson JD. 1999. Neural-tube defects. N Engl J Med 341:1509–1519.

Brocks D, Irons M, Sadeghi-Najad A, McCauley R, Wheeler P. 2000. Gomez-Lopez-Hernandez syndrome: Expansion of the phenotype. Am J Med Genet 94:405–408.

Chartier A, Martinot A, Dhellemmes P, Vallée L, Lamblin MD, Goran C, Leclerc F. 2002. Malformation de Chiari de type I de l'enfant: Modes de révélation de 34 observations. Arch Pédiatr 8:789–796.

Coppola G, Muras I, Pascotto A. 2000. Pontocerebellar hypoplasia type 2 (PCH2): Report of two siblings. Brain Dev 22:188–192.

Coppola G, Vjaro P, De Virgiliis S, Ciccimarra E, Boccone L, Pascotto A. 2002. Cerebellar vermis defect, oligophrenia, congenital ataxia, and hepatic fibrocirrhosis without coloboma and renal abnormalities: Report of three cases. Neuropediatrics 33:180–185.

Delague V, Bareil C, Bouvagnet P, Salem N, Chouery E, Loiselet J, Mégargané A, Claustres M. 2001. Nonprogressive autosomal recessive ataxia maps to chromosome 9q34-9qter in a large consanguineous Lebanese family. Ann Neurol 50:250–253.

Demaerel P. 2002. Abnormalities of cerebellar foliation and fissuration: Classification, neurogenetics and clinicoradiological correlations. Neuroradiology 44:639–646.

Dhillon AS, Chapman S, Milford DV. 2001. Cerebellar defect associated with Schimke immuno-osseous dysplasia. Eur J Pediatr 160:372–374.

Dilber E, Aynaci FM, Ahmetogllu A. 2002. Pontocerebellar hypoplasia in two siblings with dysmorphic features. J Child Neurol 17:64–66.

Gardner RJM, Coleman LT, Mitchell LA, Smith LJ, Harvey AS, Scheffer IE, Storey E, Nowothny MF, Sloane RA, Lubitz L. 2001. Near-totel absence of the cerebellum. Neuropediatrics 32:62–68.

Glickstein M. 1994. Cerebellar agenesis. Brain 117:1209–1212.

Grosso S, Mostadini R, Cioni M, Galluzzi P, Morgese G, Balestri P. 2002. Pontocerebellar hypoplasia type 2: Further clinical characterization and evidence of positive response of dyskinesia to levodopa. J Neurol 249:596–600.

Hottinger-Blanc PMZ, Ziegler AL, Deonna T. 2002. A special type of head stereotypies in children with developmental (cerebellar) disorder: Description of 8 cases and literature review. Eur J Paediatr Neurol 6:1443–1152.

Hoveyda N, Shiled JPH, Garrett C, "Kling"Chong WK, Beardsall K, Bentsi-Enchill E, Mallya H, Thompson MH. 1999. Neonatal diabetes mellitus and cerebellar hypoplasia/agenesis: Report of a new recessive syndrome. J Med Genet 36:700–704.

Johnsen SD, Tarby TJ, Lewis KS, Bird R, Prenger E. 2002. Cerebellar infarction: An unrecognised complication of very low birthweight. J Child Neurol 17:320–324.

Joubert M, Eisenring JJ, Robb JP, Andermann F. 1969. Familial agenesis of the cerebellar vermis: A syndrome of episodic hyperpnea, abnormal eye movements, ataxia, and retardation. Neurology 19:813–825.

Keuth B, Alon U, Fuchshuber A, Michalk D, Querfeld U. 1996. Aplasia of the cerebellar vermis associated with chronic renal disease. A report of six cases and a review of the literature. Eur J Pediatr 155:963–967.

Leech RW, Johnson SH, Brumback RA. 1997. Agenesis of cerebellum associated with arrhinencephaly. Clin Neuropathol 16:90–97.

Leestma JE, Torres JV. 2000. Unappreciated agenesis of cerebellum in an adult. Case report of a 38-year-old man. Am Forensic Med Pathol 21:155–11.

Leiz S, Ruedisser K, Hohnecker A, Baumeister FAM, Hoepner F, Egger J. 2000. Rhombencephalosynapsis: A rare brain malformation. Neuropediatrics 31:A33.

Madsen JR, Poussain TY, Barnes PD. 2002. Congenital malformations of the cerebellum and posterior fossa. In: Manto MU, Pandolfo M, editors. The cerebellum and its disorders. Cambridge: University Press. pp 161–177.

Mancini J, Lathel V, Hugonenq C, Charbol B. 2001. Brain injuries in early foetal life: Consequences for brain development. Dev Med Child Neurol 43:52–55.

Maria BL, Boltshauser E, Palmer SC, Tran TX. 1999a. Clinical features and revised diagnostic criteria in Joubert syndrome. J Child Neurol 14:583–590.

Maria BL, Quisling RG, Rosainz LC, Yachnis AT, Gitte J, Dede D, Fennell E. 1999b. Molar tooth sign in Joubert syndrome: Clinical, radiologic, and pathologic significance. J Child Neurol 14:368–376.

Muntoni F, Goodwin F, Sewy C, Cox P, Cowan F, Airaksinen E, Patel S, Ignatius J, Dubowitz V. 1999. Clinical spectrum and diagnostic difficulties of infantile ponto-cerebellar hypoplasia type 1. Neuropediatrics 30:243–248.

Nystuen A, Benke PJ, Merren J, Stone EM, Sheffield VC. 1996. A cerebellar ataxia locus identified by DNA pooling to search for linkage disequilibrium in an isolated population from the Cayman Islands. Hum Mol Genet 5:525–531.

Patel S, Barkovich AJ. 2002. Analysis and classification of cerebellar malformations. AJNR 23:1074–1087.

Riccardi VM, Marcus ES. 1978. Congenital hydrocephalus and cerebellar agenesis. Clin Genet 13 :443–447.

Robins JB, Mason GC, Watters J, Martinez D. 1998. Case report: Cerebellar hemi-hypoplasia. Prenat Diagn 18:173–177.

Rossi A, Bava GL, Biancheri R, Tortori-Donati P. 2001. Posterior fossa and arterial abnormalities in patients with facial capillary haemangioma: Presumed incomplete phenotypic expression of PHACES syndrome. Neuroradiology 43:934–940.

Saar K, Al-Fazali L, Sztriha L, Rueschendorf F, Nur-E-Kamal M, Reis A, Bayoumi R. 1999. Homozygosity mapping in families with Joubert syndrome identifies a locus on chromosome 9q34.3 and evidence for genetic heterogeneity. Am J Hum Genet 65:1666–1671.

Sarnat HB. 1992. Cerebral dysgenesis: Embryology and clinical expression. New York, Oxford: Oxford University Press.

Satran D, Perpont ME, Dobyns WB. 1999. Cerebello-oculo-renal syndromes including Arima, Senior-Loken and COACH syndromes: More than just variants of Joubert syndrome. Am J Med Genet 29:459–469.

Sener RN, Jinkins JR. 1993. Subtotal agenesis of the cerebellum in an adult. MRI demonstration. Neuroradiology 35:285–287.

Sener RN. 1995. Cerebellar agenesis versus vanishing cerebellum in Chiari II malformation. Comput Med Imaging Graph 19:491–494.

Sergi C, Hentze S, Sohn C, Voigtlaender T, Jung C, Schmitt HP. 1997. Telencephalosynapsis (synencephaly) and rhombencephalosynapsis with posterior fossa ventriculocele (Dandy-Walker cyst): An unusual aberrant syngenetic complex. Brain Dev 19:426–432.

Steinlin M, Schmid M, Landau K, Boltshauser E. 1997. Follow-up in children with Joubert syndrome. Neuropediatrics 28:204–211.

Steinlin M. 1998. Non-progressive congenital ataxias. Brain Dev 20:199–208.

Steinlin M, Styger M, Boltshauser E. 1999. Cognitive impairments in patients with congenital nonprogressive cerebellar ataxia. Neurology 53:966–973.

Sutton LN, Adzick NS, Bilaniuk LT, Johnsen MP, Crombleholme TM, Flake AW. 1999. Improvement in hindbrain herniation demonstrated by serial fetal magnetic resonance imaging following fetal surgery for myelomeningocele. J Am Med Assoc 282:1826–1831.

Toelle SP, Yalcinkaya C, Kocer N, Deonna T, Overweg-Plandsoen WCG, Bast R, Kalmanchey R, Barsi P, Schneider JFL, Capone Mori A, Boltshauser E. 2002. Rhombencephalosynapsis: Clinical findings and neuroimaging in 9 children. Neuropediatrics 33:209–214.

Tulipan N, Hernanz-Schulman M, Lowe LH, Brunner JP. 1999. Intrauterine myelomeningocele repair reverses preexisting hindbrain herniation. Pediatr Neurosurg 31:137–142.

Uhl M, Pawlik H, Laubenberger J, Darge K, Baborie A, Korinthenberg R, Langer M. 1998. MR findings in pontocerebellar hypoplasia. Pediatr Radiol 28:547–551.

Van Coster RN, De Praeter CM, Vanhaesebrouck PJ, Leroy JG. 1998. MRI findings in a neonate with cerebellar agenesis. Pediatr Neurol 19:139–142.

Velioglu SK, Kuzeyli K, Oezmenoglu M. 1998. Cerebellar agenesis: A case report with clinical and MR imaging findings and a review of the literature. Eur J Neurol 5:503–506.

Wang VY, Zoghbi HY. 2001. Genetic regulation of cerebellar development. Nat Rev/Neurosci 2:484–491.

Wurst W, Bally-Cuif L. 2001. Neural plate patterning: Upstream and downstream of the isthmic organizer. Nat Rev/Neurosci 2:99–108.