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NEUROANATOMY

The cerebellum is one of the first brain structures to begin to differentiate, yet it is one of the last to achieve maturity — the cellular organization of the cerebellum continues to change for many months after birth. This protracted developmental process creates a special susceptibility to disruptions during embryogenesis and makes the cerebellum highly amenable to study. Over the past few years, genetic research has provided a great deal of information about the molecular events directing the formation of the cerebellum. Knowledge of these mechanisms should enable us to address the nature of human diseases that have their root in developmental processes.

The cerebellum represents 10% of the brain's total volume, but contains more than half of our neurons. It acts as a coordination centre, using sensory inputs from the periphery to fine-tune our movement and balance. It is one of the first structures in the brain to begin to differentiate, but one of the last to mature, and its cellular organization continues to change for many months after birth. The study of mouse homologues of *Drosophila* genes has provided valuable insights into the molecular basis of cerebellar development.

In humans, the cerebellum develops from the dorsal region of the posterior neural tube, and its cells arise from two germinal matrices. Most cells are derived from the ventricular zone, but the granule neurons come from a specialized germinal matrix called the rhombic lip.

The mesencephalon and metencephalon both contribute to the developing mouse cerebellum. The patterning of these two regions depends on signals from the isthmus organizer (IO), located just caudal to their junction. *Otx2* and *Gbx2* are central to IO development. *Otx2* is expressed in the mesencephalon, with a posterior boundary at the rostral metencephalon; *Gbx2* is expressed in the metencephalon, and its anterior boundary abuts the *Otx2* boundary. Reciprocal repression maintains a sharp boundary between these domains. *Otx2*and *Gbx2* form part of a regulatory loop that includes *Wnt1*, *En1* and *Fgf8*. Many other genes, including members of the Pax and Hox families, are also involved in patterning this region.

Purkinje cells (PCs), Golgi neurons, stellate and basket cells all arise from the ventricular neuroepithelium. PCs are born around embryonic day 13, and they migrate along radial glial fibres into the cerebellar anlage. During their final maturation phase, PCs develop extensive dendritic arbors and synapse onto granule neurons. This depends on granule neuron signals, probably including *Wnt3*. Various growth factors are required for PC survival, including nerve growth factor, acetylcholine, neurotrophin 4/5, brain-derived neurotrophic factor and ciliary neurotrophic factor.

The rhombic lip, located between the fourth ventricle and the metencephalic roof plate, gives rise to granule neurons. Proliferation in its germinal epithelium is governed by the *Math1*gene. Rhombic lip cells migrate to the cerebellar anlage and settle on its periphery to form the external granule layer, another zone of proliferation. As the cells begin to migrate, they express markers that include *RU49/Zipro1*, *Zic1*and *Zic3*. *RU49/Zipro1* and *Zic1* are thought to be involved in cell proliferation, which requires interaction with PCs. PCs might release a diffusible factor such as sonic hedgehog (Shh), and *Zic1* could control cell proliferation by indirectly regulating the S*hh* pathway. The final stage of granule neuron maturation occurs after precursor cell migration into the inner granule layer.

Many genes, including *En1*, *En2*, *Pax2*, *Wnt7b*, and some of the ephrins and their receptors, show characteristic patterns of spatial expression in the cerebellum, but only *En2* has been studied specifically for its role in compartmentalization. In addition to the patterning genes, several other gene families, such as the heat shock proteins and proteins involved in neuronal migration, are also expressed in specific patterns. Spatial- and temporal-specific knockout strategies should yield more information about the roles of these genes in patterning the cerebellum.

The mature cerebellum has exquisite, stereotypical morphology, foliation, and lamination, which are consistent between individuals and highly conserved across vertebrates. At the cellular level, unlike other regions of the CNS, the cerebellum is composed of very few neuronal types, each with distinct morphology, arranged in discrete lamina, and connected in stereotypical circuits . The cerebellum has essential roles in motor coordination, but is not essential for viability. Thus, compared with other regions of the central nervous system (CNS) the cerebellum has been more amenable to genetic studies since disruptions in development, which lead to abnormal morphology or function, are readily observed in obvious neurological and behavioral phenotypes. Because of this, it has been possible to obtain a precise understanding of cerebellar development [[10](" \l "R10)–[14](" \l "R14)]. The mechanisms deciphered from the study of cerebellar development have broad applicability to other CNS regions such as the cerebral cortex. For example, while initial insights regarding the function of the Reelin gene were gleaned from studying the cerebella of reeler mice recent studies have revealed that this gene is required for the emigration of dentate gyrus progenitors from a transient subpial zone and into the subgranular zone .Also, while Foxc1 controls normal cerebellar and posterior fossa development by regulating secreted growth factor signals from the mesenchyme ; , it is also required for the development of meningeal structures that in turn influence skull and cortical development .

THE GENETIC BASES OF CEREBELLAR DISORDERS are:

Causes of unilateral cerebellar abnormality

In 16 patients with asymmetrical abnormalities, extensive unilateral hypoplasia of one cerebellar hemisphere was found in 11 patients, whereas minor structural lesions were present in the other five. No evidence was found in any of the patients for a genetic or neurodegenerative cause.

Unilateral cerebellar hypoplasia in two male patients from unrelated families was accompanied by microcephaly, severe psychomotor retardation with autistic features, and ipsilateral choroideo-retinal coloboma. The cause of this disorder in these sporadic cases remains unknown. In the other nine patients with unilateral cerebellar hypoplasia the following related or unrelated conditions were present: one patient had a combination of meningomyelocele, holoprosencephaly and Chiari type IV malformation; one patient suffered from mental retardation and showed craniofacial dysplasia with callosal agenesis; one patient had status epilepticus at the age of 3 years, and unilateral hypoplasia was discovered by chance. Her sister’s daughter suffered from acro-callosal syndrome (see below). In six other patients severe pre-or perinatal hypoxic ischaemia or traumatic events had caused unilateral infratentorial damage. The five patients with minor unilateral cerebellar lesions had suffered from cerebellitis (one patient), cerebellar stroke (two patients), whereas cerebellar pathology was probably unrelated in one patient with intractable epilepsy and in one patient with congenital muscular dystrophy.

Causes of pontocerebellar hypoplasia

The diagnoses for our patients with midline or bilateral (ponto-) cerebellar structural abnormalities are the presence of pontine hypoplasia combined with cerebellar hypoplasia or atrophy was delineated as a separate group of disorders in nine patients. Four different autosomal recessive syndromes have been recognized in seven of these patients, i.e. carbohydrate-deficient glycoprotein syndrome type I in two siblings, pontocerebellar hypoplasia type I (one patient) and type II (three patients) and the progressive encephalopathy with hypsarrhythmia and optic atrophy syndrome in one patient. One child of dizygotic twins was born prematurely and sustained septicaemic shock resulting in severe pontomedullo-cerebellar atrophy. The diagnosis remained unclear in one child from a family of non- consanguineous parents manifesting progressive micro- cephaly, neurodevelopmental delay and pontocerebellar atrophy.

The carbohydrate-deficient glycoprotein syndrome type I was diagnosed in two siblings with marked phenotypical variability. The boy (aged 14 years) suffered from profound mental retardation since early infancy and could not walk independently. The main clinical findings included

Serum transferrin isoelectric focusing for detection of carbohydrate-deficient glycoprotein syndrome type I; transferrin is a glycoprotein onto which two antennae-like saccharide side- chains are attached, each of which contains either two or three end-standing sialic acid residues. These negatively charged sialic acid residues can be used to differentiate between the different transferrin moieties. Lanes A–D are from healthy controls (C and D are from the parents of the described patients), in which the normal transferrin molecule pattern with four to six sialic acid residues can be seen; much less intense bands can sometimes be seen for the disialo- and trisialo-transferrin moieties due to normal transferrin heterogeneity. Lanes E–I show the patterns typical for carbohydrate-deficient glycoprotein syndrome type I (those of the described male and female siblings with carbohydrate-deficient glycoprotein syndrome are shown in lanes E and F). In patients there is a shift of the transferrin pattern with some loss of the tetrasialo-transferrin band and typical appearance of asialotransferrin and disialotransferrin moieties.

parkinsonian features, severe ataxia, kyphoscoliosis and a peripheral neuropathy. Neuroimaging showed extensive bilateral cerebellar hypoplasia and mild pontomedullary hypoplasia. His sister had only moderate mental retardation and was able to speak, write and read. On examination she only showed discrete signs of ataxia. Compared with the MRI of her brother, the pontomedullary and cerebellar hypoplasia was less marked. Both children had only minor dysmorphic features on physical examination, not suggesting the carbohydrate-deficient glycoprotein syndrome. There were no differences regarding the serum glycoprotein levels or the sialotransferrin pattern

In one patient, the autosomal recessively transmitted pontocerebellar hypoplasia type I was diagnosed. Since birth he suffered from the Werdnig–Hoffmann type spinal muscular atrophy associated with pontocerebellar hypoplasia on neuro-imaging.

A diagnosis of pontoneocerebellar hypoplasia type II could be confirmed in three unrelated children by the typical clinical history and MRI findings. This autosomal recessive condition is of prenatal onset with severe feeding difficulties in the neonatal period followed by severe psychomotor delay, microcephaly and extrapyramidal dyskinesia with chorea. Another differential diagnostic feature from type I is the absence of spinal muscular atrophy. MRI shows distinctive features of pontine hypoplasia with a preserved vermis, but only small remnants for both cerebellar hemispheres

Genetic disorders and cerebellar abnormalities in childhood

Autosomal recessive pontocerebellar hypoplasia type 2 is a prenatal onset condition with severe neurodevelopmental delay,

microcephaly, extrapyramidal features and the absence of spinal muscular atrophy. Pontine hypoplasia with a preserved vermis can be

seen on sagittal T -weighted images, while bilateral cerebellar hypoplasia is present on a coronal section (right side of the figure

One child fullfilled the diagnostic criteria for the progressive encephalopathy with hypsarrhythmia and optic atrophy syndrome: (i) infantile hypotonia; (ii) infantile spasms and myoclonic fits with hypsarrhythmia starting at the age of 3 months; (iii) profound psychomotor retardation and severe hypotonia; (iv) early onset of bilateral optic atrophy with loss of visual fixation; and (v) progressive infratentorial pontine, brainstem and cerebellar atrophy.

Causes of midline (vermis) structural changes

Among the different structural abnormalities affecting the cerebellar midline structures in 15 patients, only four conditions with typical clinical features and constant structural changes of the vermis and midbrain were found. Only Joubert and Gillespie syndrome are autosomal recessive, while Cogan’s oculomotor apraxia and anorexia nervosa occur sporadically or are acquired conditions.

In three patients complete vermis agenesis with a typical neonatal history of hyperpnoea–apnoea and ocular nystagmus followed by severe neurodevelopmental delay, ataxia and episodes of hyperventilation enabled us to diagnose Joubert’s

syndrome. Another autosomal recessive but rare condition was found in one patient with Gillespie’s syndrome, manifesting the combination of mental retardation, ataxia and aniridia.

Vermis and midbrain dysgenesis was associated with Cogan’s congenital oculomotor apraxia and moderate psychomotor retardation in two patients. Cogan’s oculomotor apraxia is considered to occur sporadically. Hypoplasia of the upper vermian structures together with thin and elongated superior cerebellar peduncles and sometimes fusion of the colliculi have been noticed in our patients as reported in the literature (Whitsel et al., 1995). Complete vermis atrophy was present in one patient with anorexia nervosa.

The other anatomical abnormalities included vermis agenesis, dysplasia, cysts, or only lower vermis agenesis/ hypoplasia, which have been described as occasional but not as constant findings in many genetic and non-genetic syndromes (Bordarier and Aicardi, 1990).

Causes of non-progressive cerebellar hypoplasia

Out of 10 patients with bilateral cerebellar hypoplasia of the non-progressive type, one had trisomie 21 and one had

1744 V. Th. Ramaekers et al.

Boucher–Neuha ̈user syndrome in a 16-year-old girl showed progressive cerebellar atrophy on follow-up neuroimaging. MRI showed cerebellar vermis atrophy with preserved pontomesencephalic structures (sagittal T -weighted images on the left), while the T -

12 weighted images in the axial planes (on the right) showed additional cerebellar hemisphere atrophy with absence of myelin signal in both

temporal lobes.

trisomie 18, and another patient suffered from the autosomal recessive acro-callosal syndrome. The CT brain scan in acro- callosal syndrome (Schinzel–Giedion syndrome) showed callosal agenesis and cerebellar hypoplasia. The main dysmorphic features included macrocephaly with a high broad forehead, hypertelorism with downslanting palpebral fissures, hypoplasic midface, posteriorly rotated and somewhat dysmorphic pinnae and protruding lips. Severe growth and mental retardation with generalized weakness and hypotonia since birth were present. Both halluces and thumbs showed partial duplications. Further investigations also revealed a congenital heart defect. Both parents were healthy but the mother’s sister had unilateral cerebellar hypoplasia, discovered by chance on CT scan after status epilepticus.

Known genetic transmission in the remaining seven patients was not present. One patient suffered from the Cornelia de Lange syndrome. In one patient with congenital cyto- megalovirus infection, severe vermis and cerebellar hypoplasia without intracranial calcifications were present. One patient had developed normally until the age of 1 year at which time she acquired aseptic meningitis and cerebellitis.

Four patients, all born prematurely after only 25–28 weeks of gestation, suffered from serious hypoxic-ischaemic encephalopathy in the perinatal period resulting in periventricular leukomalacia and cerebellar atrophy.

Causes of progressive cerebellar atrophy

A genetic cause was found in 20 out of 28 patients with progressive cerebellar atrophy. In 19 patients the genetic transmission was autosomal recessive, while in one girl with pyruvate dehydrogenase deficiency, transmission proved to be X-linked. In the remaining group of eight patients no known genetic factor could be established.

In the 20 inherited cases, the clinical features and additional investigations elucidated the cause. One girl was described as floppy with severe developmental delay since birth. Seizures started from the age of 4 months. At that time episodes of lactic acidosis and coma occurred. The CT scan of the brain showed bilateral cerebellar hypoplasia with pericerebellar cyst-like extensions, callosal agenesis and severe supratentorial loss of brain parenchyma. Enzymatic assay on fibroblasts confirmed severe pyruvate dehydrogenase (PDH) deficiency. A single base mutation was found at the second regulatory phosphorylation site in exon 10 of the PDH E1- α gene, i.e. a TGT transition from the normal CGT, causing a cystein substitution for arginine at amino acid position 300 of the E1-α gene (De Meirleir et al., 1993). Another patient with similar clinical and CT findings, suffered from partial PDH and cytochrome oxidase deficiency.

One child from consanguineous parents (first cousins) presented with myoclonic seizures from the age of 18 months, followed by a rapidly downhill course with loss of motor.

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Genetic disorders and cerebellar abnormalities in childhood 17