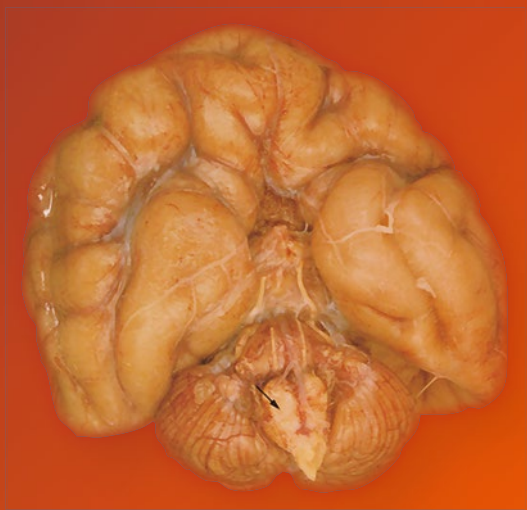
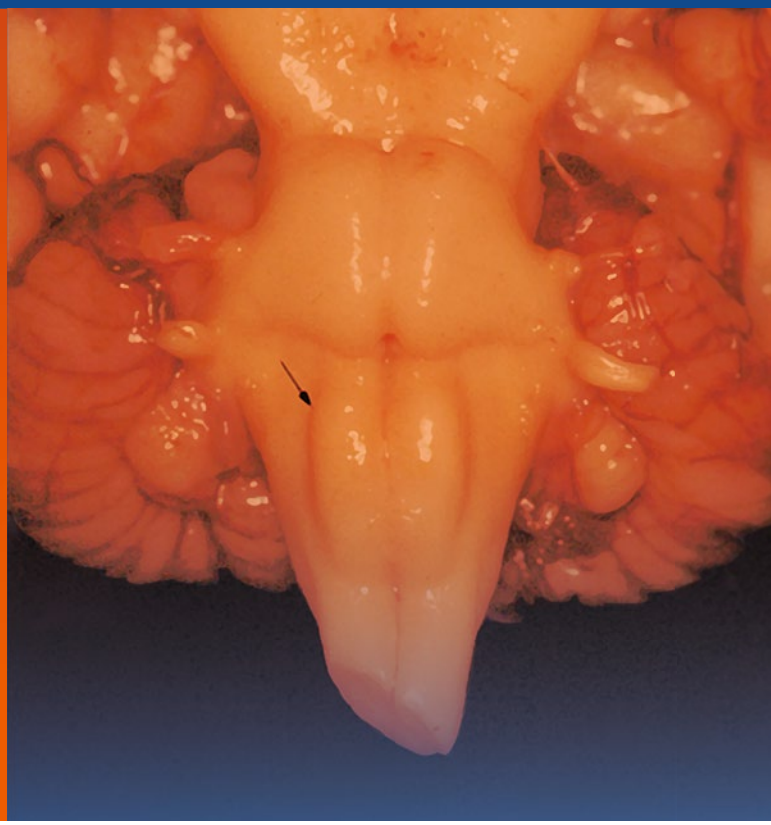


Hans J. ten Donkelaar
Martin Lammens
Akira Hori



Clinical Neuroembryology

Development and Developmental Disorders of the Human Central Nervous System

Second Edition

Springer

Clinical Neuroembryology

Hans J. ten Donkelaar • Martin Lammens
Akira Hori

Clinical Neuroembryology

Development and Developmental Disorders of the Human Central Nervous System

Second Edition

In co-operation with:

Eleonora Aronica
Mireille Bekker
Johannes R.M. Cruysberg
Kyoko Itoh
Karin Kamphuis-van Ulzen
Irene M.J. Mathijssen
Ronald Pennings
Willy O. Renier
Kohei Shiota
Hans van Bokhoven
Ton van der Vliet
Patrick van der Voorn
John M.G. van Vugt
Christl Vermeij-Keers
Pieter Wesseling
Michèl Willemsen
Shigehito Yamada

Springer

Hans J. ten Donkelaar, M.D., Ph.D.
935 Department of Neurology
Radboud University Nijmegen Medical Centre
Nijmegen, The Netherlands

Martin Lammens, M.D., Ph.D.
Department of Pathology
University Hospital Antwerpen
Edegem, Belgium

Akira Hori, M.D., Ph.D.
Institute of Pathology
Medizinische Hochschule Hannover
Hannover, Germany

Research Institute for Longevity Medicine
Fukushimura Hospital
Toyohashi, Japan

ISBN 978-3-642-54686-0 ISBN 978-3-642-54687-7 (eBook)
DOI 10.1007/978-3-642-54687-7
Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2014940543

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface to the Second Edition

Apart from a general updating of the extensive literature on developmental neurobiology, neurogenetics, imaging and developmental neuropathology between 2005 and 2013, more emphasis has been given to: (a) imaging of the embryonic brain (early prenatal diagnosis by ultrasound); (b) imaging of the fetal brain by MRI; (c) DTI studies on the development of major fibre connections such as the pyramidal tract and the corpus callosum; and (d) the impact of newer genetic techniques such as whole exome/genome sequencing. Moreover, new classifications of brain disorders have been implemented such as a new classification of midbrain-hindbrain developmental disorders and entire new families of disorders such as ciliopathies and dystroglycanopathies. Throughout the book, several new Clinical Cases have been added.

Several colleagues kindly contributed as new co-authors their expertise to this second edition, including Eleonora Aronica (Amsterdam), Mireille Bekker (Nijmegen), Kyoko Itoh (Kyoto), Karin Kamphuis-van Ulzen (Nijmegen), Irene Mathijssen (Rotterdam), Ronald Pennings and Hans van Bokhoven (Nijmegen), Patrick van der Voorn (Amsterdam) and Shigehito Yamada (Kyoto). They also contributed new Clinical Cases. For other new Clinical Cases, the help of Remke Dullemond (Rotterdam), Janet Eyre (Newcastle), Floris Groenendaal (Utrecht), Gregor Kasprian (Vienna), Hajime Miyata (Akita), Peter Nikkels (Utrecht), Tetsu Niwa (Yokohama), Andrea Poretti (Zurich), Ritsuko Pooh (Osaka), Goran Simić (Zagreb) and Marjolein Willemsen (Nijmegen) is gratefully acknowledged. New illustrations were also kindly provided by Marco Catani and Michel Thiebaut de Schotten (London), Cyrille Ferrier (Utrecht), Hao Huang (Dallas), Ole Kiehn (Stockholm), Grace Lai (New York), Anna Lavezzi (Milan) and Maria Thom (London). A long weekend with Luis Puelles in Murcia greatly helped the first author to implement new findings on the prosomeric model of the developing brain.

Hans J. ten Donkelaar, Nijmegen
Martin Lammens, Edegem
Akira Hori, Toyohashi

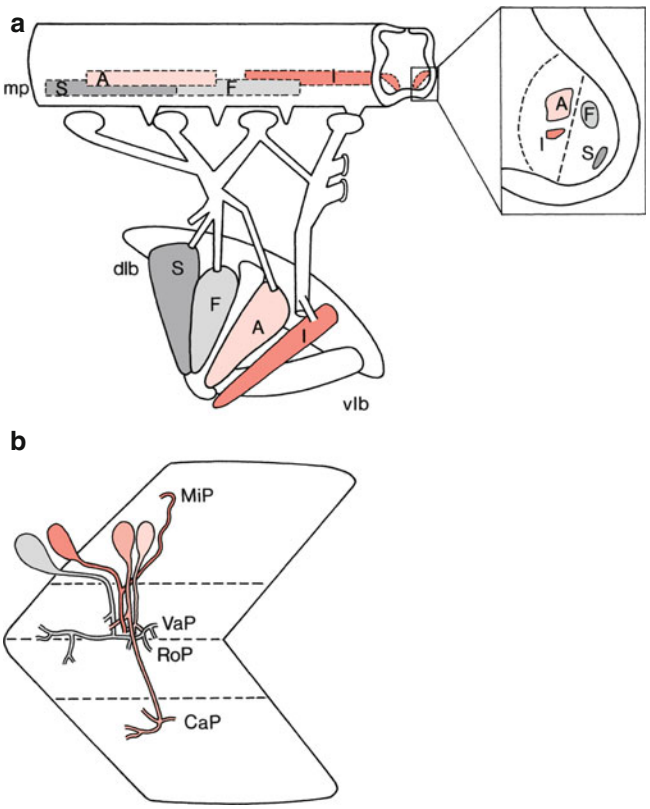


Fig. 6.10 Organization of motor pools in the chick hindlimb (**a**) and primary motoneurons (**b**) in the zebrafish. (**a**) Motor pools (*mp*) of the sartorius (*S*), femorotibialis (*F*), adductor (*A*) and ischioflexor (*I*) muscles and their targets are shown in different colours. (**b**) Primary motoneuron types, characterized by different *LIM3* and *Isl1/2* codes, are shown for one neuromuscular segment. *CaP* caudal primary motoneuron, *dlb* dorsal limb, *MiP* medial primary motoneuron, *RoP* rostral primary motoneuron, *VaP* variable type of primary motoneuron, *vlb* ventral limb (After Pfaff and Kintner 1998)

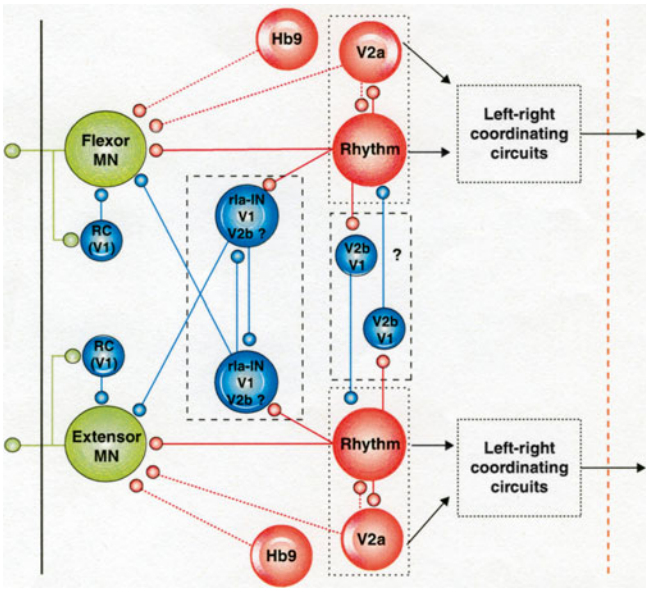


Fig. 6.11 Diagram of the rodent CPG. Flexor and extensor motoneurons (*MNs*) are driven to rhythmicity by alternating excitation and inhibition. Excitatory rhythm-generating neurons, therefore, need to drive premotor inhibitory neurons. Candidate premotor inhibitory neurons are Ia-interneurons connected in a reciprocal pattern belonging to the V1 population and possibly the V2b population (*rIa-IN*, *V1*, *V2b*?), and non-reciprocal group I-interneurons (not indicated). Some rhythmic premotor inhibition is also mediated via crossed connections and V1-related Renshaw cells (*RC*) activity. V2a-interneurons have connections to motoneurons. Other types of ipsilateral excitatory neurons besides the V2 neurons generate the rhythm and the drive to motoneurons, directly and indirectly. These include Hb9 and ipsilateral V3 interneurons. The rhythm-generating core and V2a-interneurons also drive the left-right coordinating circuits. Some hypothetical inhibitory reciprocal connections between flexor and extensor rhythm-generating modules may serve a distinct role in securing flexor-extensor alternation (*V1*, *V2b*?) (After Kiehn 2011; kindly provided by Ole Kiehn, Stockholm)

in contrast to *Netrin-1* and *DCC* mutants (Rabe Bernhardt et al. 2012). Mutations in *DCC* in humans cause congenital mirror movements (Sect. 6.7.4).

Motoneuron diseases (***MNDs***) form an etiologically heterogeneous group of disorders characterized by muscle weakness and/or spastic paralysis, which results from the selective degeneration of lower motoneurons (spinal and bulbar motoneurons) and/or upper motoneurons (corticospinal neurons). The MNDs include the adult-onset amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS) and spinal bulbar muscular atrophy (SBMA), hereditary spastic paralysis and spinal muscular atrophy, both arising from early childhood onwards, and the fetal MND lethal congenital contracture syndrome (LCCS). ***Spinal muscular atrophy*** (***SMA***) is an autosomal recessive MND and is one of the most common genetic diseases that cause infant mortality (Lorson et al. 1998). SMA is characterized by the loss of spinal anterior horn cells, hypotonia and progressive denervation of skeletal muscles (Dubowitz 1995; Simić et al. 2008) and is classified into several types (Clinical Case 6.1).

The various manifestations of ***hereditary spastic paraplegia*** (***HSP***) comprise, after ALS, the second most important group of MNDs. The various spastic paraplegia (SPG) loci are associated with different forms of HSP (reviewed in Dion et al. 2009). SPG types relate to axonal transport and membrane trafficking, mitochondrial dysfunction, Schwann cell-related HSP and other cellular dysfunctions. Two HSP causitive genes for the L1 cell adhesion molecule (L1CAM) and the proteolipid protein 1 (PLP1) underlie two X-linked forms of HSP (Jouet et al. 1994; Saugier-Veber et al. 1994). The *L1CAM*-associated HSP (SPG1) is the most common form of complicated HSP. The transmembrane protein L1CAM is expressed in neurons and Schwann cells and may have a role in the development of the CNS (Hortsch 2000). Mutations in *PLP1*, associated with SPG2, have been found in families with complicated HSP and also cause Pelizaeus-Merzbacher disease (Inoue 2005; Chap. 2). *L1CAM* mutations are further discussed in Sect. 6.7.4.

Degeneration of spinal motoneurons is also one of the characteristics of the ***lethal congenital contracture syndrome*** (***LCCS***) as shown in Clinical Case 6.2.

Clinical Case 6.1. Spinal Muscular Atrophy

Spinal muscular atrophy (***SMA***) is an autosomal MND characterized by the loss of spinal anterior horn cells, hypotonia and progressive denervation of skeletal muscles. According to age at onset and severity, SMA is classified in several types (Dubowitz 1995):

1. SMA-I (Werdnig-Hoffmann disease, acute SMA) with onset usually before 9 months; the affected infants fail to achieve early motor milestones, are never able to sit and usually die within the first 2 years of life after respiratory failure;
2. SMA-II, the intermediate or chronic infantile form, with onset around 3–15 months; children with SMA-II may sit but do not learn to ambulate;
3. SMA-III (Kugelberg-Welander disease) with onset between 1 and 15 years; these children are able to achieve walking and generally live into adulthood;
4. SMA-IV, a rare adult form with onset after 30 years of age.

SMA types I-III are all caused by loss-of-function mutations or deletions of *SMN1* on chromosome 5q13 (Lefebvre et al. 1995). The SMN protein is most abundant in the cytoplasm of α-motoneurons (Battaglia et al. 1997). Together with the degeneration and subsequent loss of anterior horn cells (α- and γ-motoneurons as well as interneurons), 'empty cell beds', glial cell bundles of ventral spinal roots, and heterotopic motoneurons (HMNs) are the most obvious neuropathological findings (Simić et al. 2008).

Simić et al. (2008) examined the occurrence and amount of HMNs in spinal cord tissue from 8 children with SMA (6 with SMA-I and 2 with SMA-II). All were carrying a homozygous deletion of exon 7 in the *SMN1* gene. All SMA subjects showed a significant number of HMNs at all levels of the spinal cord. Heterotopic neurons were hyperchromatic, located mostly in the ventral white matter and had no axon or dendrites (Fig. 6.12). More than half of the HMNs were very undifferentiated, as shown by their lack of immunoreactivity for NeuN and MAP2 proteins. With in situ end labelling (ISEL) HMNs in the ventral outflow were found to die by necrosis. Simić et al. (2008) suggested that abnormal migration, differentiation and lack of axonal outgrowth may induce motoneuron apoptosis, predominantly during early stages, whereas a slower necrosis-like cell death of displaced motoneurons which 'escaped' apoptosis characterizes later stages of SMA.

This case was kindly provided by Goran Simić (Department of Neuroscience, Croatian Institute for Brain Research, Medical School of Zagreb, Croatia).

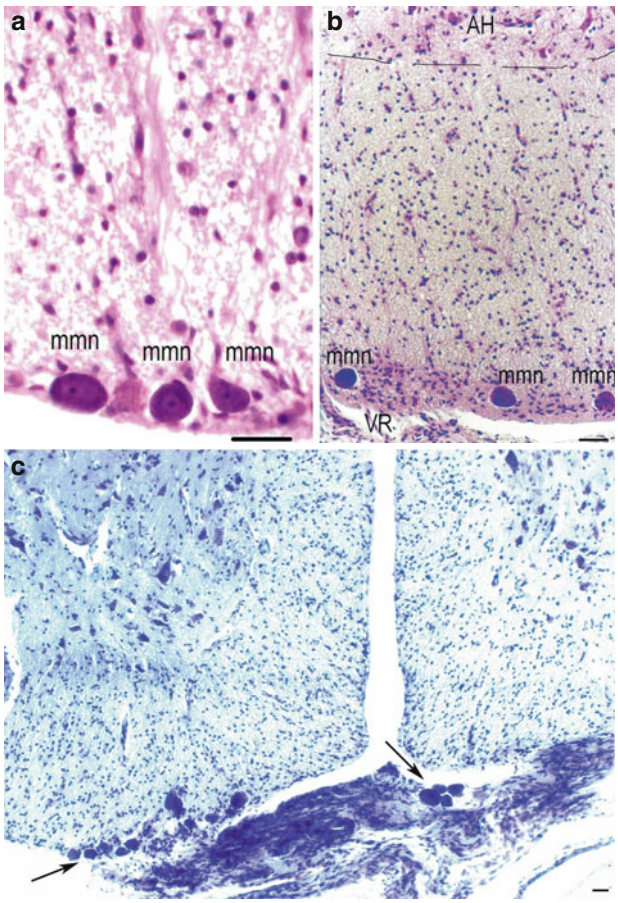


Fig. 6.12 Accumulation of heterotopic (migratory) motoneurons (*mmn*) at the anterior rim of the spinal cord in: (**a**) a female 5-month-old SMA-I subject, (**b**) a male 8-month-old SMA-I subject, and (**c**) in some sections, particularly those of younger SMA-I subjects, more than ten heterotopic motoneurons 'aligned' at the front wall of the spinal cord (*lower left corner arrow*) or outside the spinal cord (*lower right corner arrow*). *AH* anterior horn, *VR* ventral root. *Scale bars* = 20 µm (From Simić et al. 2008; kindly provided by Goran Simić, Zagreb)

References

Battaglia G, Princivalle A, Forti F, Lizier C, Zeviani M (1997) Expression of the SMN gene, the spinal muscular determining gene, in the mammalian central nervous system. Hum Mol Genet 6:1961–1971

Dubowitz V (1995) Disorders of the lower motor neuron, the spinal muscular atrophy. In: Dubowitz V (ed) Muscle disorders in childhood. Saunders, Philadelphia, pp 325–369

Lefebvre S, Burglen L, Reboullet S, Clermont O, Burlet P, Viollet L, et al. (1995) Identification and characterization of a spinal muscular atrophy-determining gene. Cell 80:155–165

Simić G, Mladinov M, Seso Simić D, Jovanov Milošević N, Islam A, Pajtak A, et al. (2008) Abnormal motoneuron migration, differentiation, and axon outgrowth in spinal muscular atrophy. Acta Neuropathol (Berl) 115:313–326

Clinical Case 6.4. *L1CAM* Mutation

L1CAM is a neural cell adhesion molecule expressed in the developing nervous system. A number of X-linked human neurological disorders with links to the *L1CAM* gene have been reported, including X-linked hydrocephalus, MASA syndrome, X-linked spastic paraplegia and CRASH syndrome (see Case Report). The phenotype common to these disorders is congenital hydrocephalus, but the underlying mechanism remains to be elucidated.

Case report. A male fetus was stillborn at the 21st week of gestation. He was the first boy with no family history. Fetal ultrasonography and MRI at the 18th week of gestation led to the prenatal diagnosis of fetal hydrocephalus with adducted thumbs, characteristic for the phenotype of an *L1CAM* mutation (Fig. 6.30a–f). The cerebral hemispheres normal convexity (Fig. 6.30g). In sections, the cerebrum showed hydrocephalus with a thin wall of the dorsal telencephalon, absence of the corpus callosum and fused thalami (Fig. 6.30h). Histologically, the cerebral cortices of the frontal, parietal, temporal and occipital lobes were normally formed. The cerebellum also showed normal cortical lamination. The genetic analysis revealed an *L1CAM* mutation at 818–820 DEL.

Unfortunately, the spinal cord could not be examined, but in the brain stem at the facial nerve level, the pyramidal tract was not evident (Fig. 6.30i) as it should have been as found in an age-matched control (Fig. 6.30j).

This case was kindly provided by Kyoko Itoh (Department of Pathology and Applied Neurobiology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Japan).

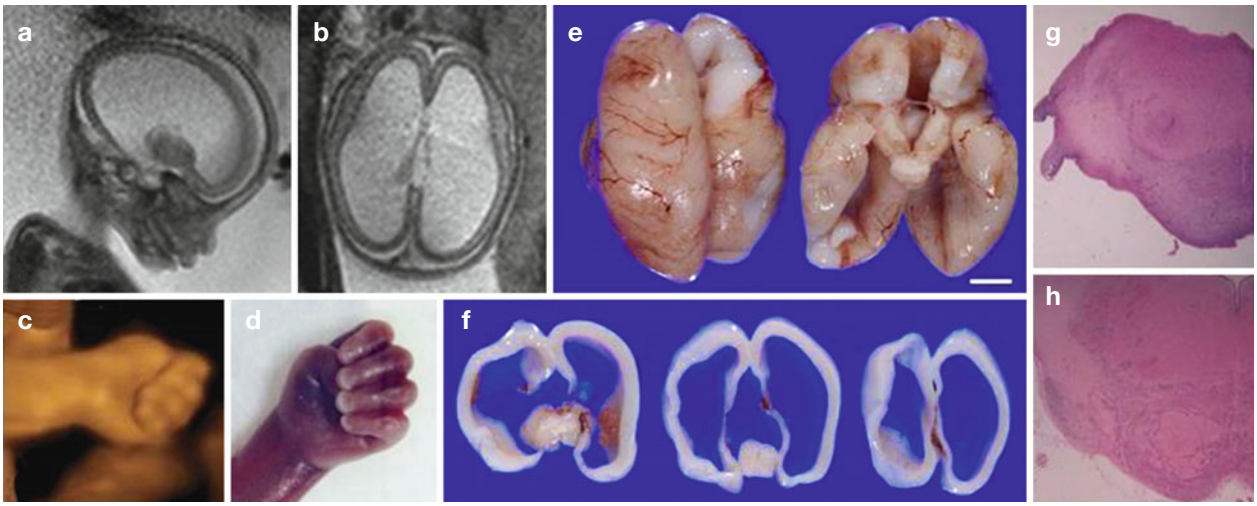


Fig. 6.30 (**a**–**d**) Fetal MRIs at the 18th week of gestation showing the extensive hydrocephalus of a L1CAM case; (**e**, **f**) 3D-ultrasound (**e**) showing the adducted thumb of the fetus, confirmed at autopsy (**f**); the cerebral hemispheres showed normal convexity (**g**); in sections (**h**), the thin wall of the telencephalon is evident as well as agenesis of the corpus callosum and fused thalami; (**i**, **j**) transverse, HE-stained sections through the brain stem at the level of the facial nerve, showing near-absence of the pyramidal tract in the L1CAM case (**i**) versus its presence in an age-matched control (**j**) (The photomicrographs were kindly provided by Kyoko Itoh, Kyoto)

6.8 Developmental Anomalies of the Spinal Cord

Developmental anomalies of the spinal cord include rare malformations such as anomalies of histogenesis, duplications, neurenteric cysts and abnormal course or even absence of fibre tracts and more common malformations such as syringomyelia. The most common malformations of the spinal cord, the neural tube defects, are discussed in Chap. 4.

6.8.1 Anomalies of Histogenesis

Small grey matter ectopia are found regularly in the spinal cord. Hori (1981, 1998) noted a frequency of 2 % in autopsies. Neuronal heterotopia in the white matter were also found incidentally in 2 % of autopsies (Hori 1981, 1998). Intramedullary heterotopic nerve cells may be more frequent in amyotrophic lateral sclerosis (Kozlowski et al. 1989; Martin et al. 1993; Sasaki and Iwata 1998). Quite often there are heterotopic nerve cells in the posterior as well as in the

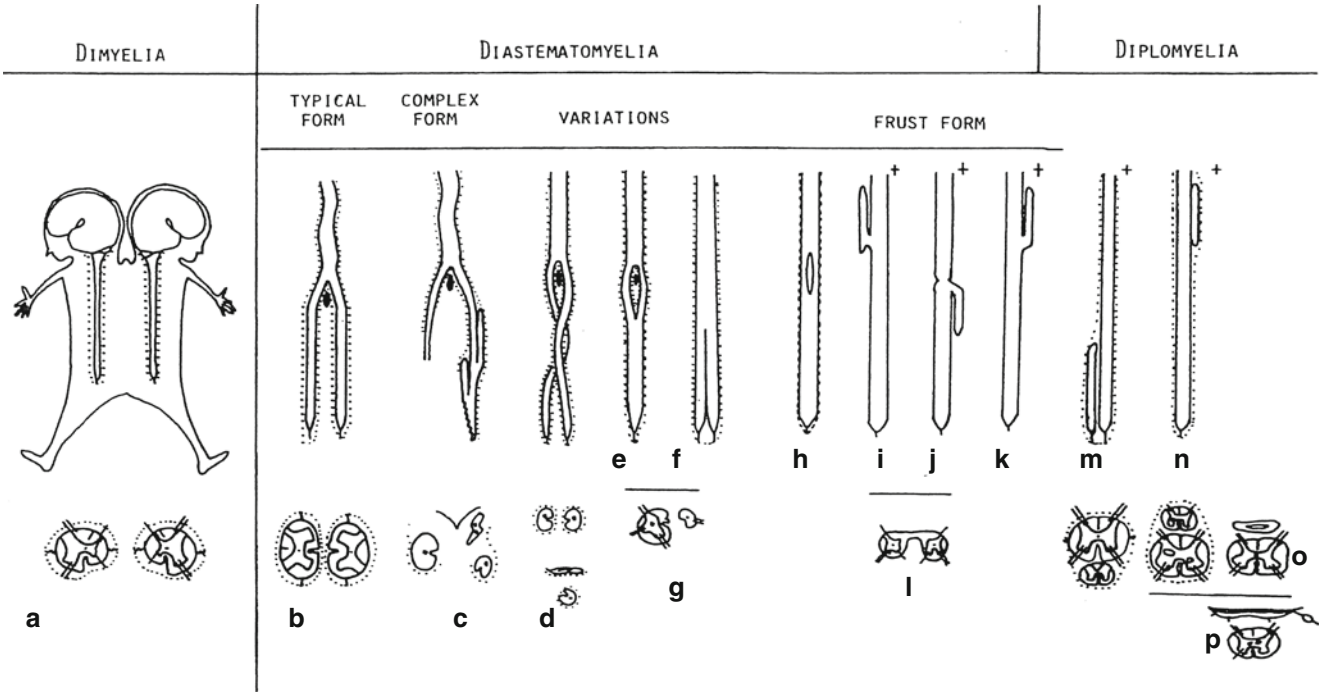


Fig. 6.31 Duplications of the spinal cord. Summary of the morphologic features of cases of dimyelia, diastematomyelia and diplomyelia: (**a**–**c**) (Hori et al. 1982); (**d**) (Rokos 1975); (**e**) (Benstead 1953); (**f**) (James and Lassman 1964); (**g**, **l**) (Emery and Lendon 1974; reverse form of (**l**) with four posterior and two anterior columns: Vinters and Gilbert 1981); (**h**) (Kersten 1954; James and Lassman 1972); (**i**) (Griepentrog 1953); (**j**) (Haas 1952); (**k**) (von Sántha 1930); (**m**) (Hori et al. 1982; Clinical Case 6.1); (**n**) (Dominok 1962); (**o**) (Környey 1925); (**p**) (Schneiderling 1938). Apart from those indicated by *crosses* (left lateral views), anteroposterior views of the spinal cord are shown. *Broken lines* indicate the dura (After Hori et al. 1982)

anterior spinal nerve roots (Hori 1988a). Heterotopic neurons in the posterior roots originate from the posterior spinal ganglion and those in the anterior roots may originate from the anterior horn as well as from the posterior spinal ganglion. Abnormal motoneuron migration, differentiation and lack of axonal outgrowth may play an important role in spinal muscular atrophy (Simić et al. 2008; Clinical Case 6.1).

6.8.2 Duplications of the Spinal Cord

Ectopic expression of *Gcm1* induces congenital spinal cord abnormalities (Nait-Oumesmar et al. 2002). Brief ectopic expression of *Gcm1* in mouse embryonic tail buds leads to spina bifida and/or multiple neural tubes. ***Duplications*** of the ***spinal cord*** are rare malformations of the human nervous system. Hori et al. (1982) described four types of total or partial duplication of the human spinal cord, using the following subdivision (Fig. 6.31): (1) dimyelia, a complete duplication of the spinal cord; (2) diplomyelia, an isolated accessory spinal cord without roots at the ventral lumbosacral level; (3) complex diastematomyelia (*diastema* is Greek for split); and (4) typical diastematomyelia. ***Dimyelia*** was observed in a female stillborn dicephalus dibrachius. Histologically, the two spinal cords showed symmetric medial hemihypoplasia that included the spinal roots (Fig. 6.31a). The term dimyelia should be restricted to cases with a total duplication of the spinal cord. ***Diplomyelia*** was found in a newborn girl with a cardiovascular malformation (Clinical Case 6.5). The term diplomyelia should be limited to cases of an isolated accessory spinal cord, ventral or dorsal to the normal cord (Környey 1925; Schneiderling 1938; Dominok 1962; Hori et al. 1982; Pang et al. 1992; Hori 1998). ***Diastematomyelia*** means a lateral bifurcation of the spinal cord, independent of whether or not the branches show completely differentiated cord structures with four columns and segmental roots. Diastematomyelia is usually associated with a bony spur or a cartilaginous or fibrous septum in the spinal canal. Typical, complex and 'forme fruste' forms can be distinguished (Fig. 6.31). A complex form was found in a 9-day-old boy with a Chiari II malformation and a thoracic meningomyelocele. The left branch of the cord showed further complex anomalies. A typical form was observed in a stillborn girl, born to an adolescent mother at 34 weeks of gestation (Fig. 6.32).

Schneiderling W (1938) Unvollkommene dorso-ventrale Verdoppelung des Rückenmarkes. Virchows Arch Pathol Anat Physiol 31:479–489

Schoenen J, Faull RLM (1990) Spinal cord: cytoarchitectural, dendroarchitectural, and myeloarchitectural organization. In: Paxinos G (ed) The human nervous system. Academic, San Diego, pp 19–53

Schreyer DJ, Jones EG (1982) Growth and target finding by axons of the corticospinal tract in prenatal and postnatal rats. Neuroscience 7:1837–1853

Schreyer DJ, Jones EG (1988) Axon elimination in the developing corticospinal tract of the rat. Brain Res Dev Brain Res 38:103–119

Schwab ME, Schnell L (1991) Channeling of developing rat corticospinal tract axons by myelin-associated neurite growth inhibitors. J Neurosci 11:709–721

Sharma K, Frank E (1998) Sensory axons are guided by local cues in the developing dorsal spinal cord. Development 125:635–643

Sharma K, Peng C-Y (2001) Spinal motor circuits: merging development and function. Neuron 29:321–324

Sherman JL, Barkovich AJ, Citrin CM (1986) The MR appearances of syringomyelia: new observations. AJNR Am J Neuroradiol 7:985–995

Sicotte NL, Salamon G, Shattuck DW, Hageman N, Rüb U, Salamon N et al (2006) Diffusion tensor MRI shows abnormal brainstem crossing fibres associated with ROBO3 mutations. Neurology 67:519–521

Silos-Santiago I, Snider WD (1992) Development of commissural neurons in the embryonic rat spinal cord. J Comp Neurol 325: 514–526

Silos-Santiago I, Snider WD (1994) Development of interneurons with ipsilateral projections in embryonic rat spinal cord. J Comp Neurol 342:221–231

Simić G, Mladinov M, Seso Simić D, Jovanov-Milošević N, Islam A, Pajtak A et al (2008) Abnormal motoneuron migration, differentiation and axon outgrowth in spinal muscular atrophy. Acta Neuropathol 115:313–326

Sims TJ, Vaughn JE (1979) The generation of neurons involved in an early reflex pathway of embryonic rat spinal cord. J Comp Neurol 183:707–720

Skandalakis JE, Gray SW (1994) Embryology for surgeons, 3rd edn. Williams & Wilkins, Baltimore

Snider WD, Zhang L, Yusoof S, Gorukanti N, Tsering C (1992) Interactions between dorsal root axons and their target motor neurons in developing mammalian spinal cord. J Neurosci 12: 3494–3508

Spiller WG (1906) Syringomyelia, extending from the sacral region of the spinal cord through the medulla oblongata, right side of the pons and right cerebral peduncle to the upper part of the right internal capsule (syringobulbia). Br Med J 2:1017–1021

Srour M, Rivière JB, Pham JM, Dubé MP, Girard S, Morin S et al (2010) Mutations in the DCC gene cause congenital mirror movements. Science 328:592

Stanfield BB (1992) The development of the corticospinal projection. Prog Neurobiol 38:169–202

Stanfield BB, O'Leary DDM (1985) The transient corticospinal projection from the occipital cortex during the postnatal development of the rat. J Comp Neurol 238:236–248

Staudt M (2010) Reorganization after pre- and perinatal brain lesions. J Anat 217:469–474

Staudt M, Grodd W, Gerloff C, Erb M, Stitz J, Kräpelin-Mann I (2002) Two types of ipsilateral reorganization in congenital hemiparesis. A TMS and fMRI study. Brain 125:2222–2237

Staudt M, Gerloff C, Grodd W, Holthausen H, Niemann G, Krägeloh-Mann I (2004) Reorganization in congenital hemiparesis acquired at different gestational ages. Ann Neurol 56:854–863

Streeter GF (1919) Factors involved in the formation of the filum terminale. Am J Anat 25:1–11

Swank RL (1934) The relationship between the circumolivary pyramidal fascicles and the pontobulbar body in man. J Comp Neurol 60:309–317

Swanson AG, Buchan GC, Alvord EC Jr (1965) Anatomic changes in congenital insensitivity to pain. Arch Neurol 12:12–18

ten Donkelaar HJ (2000) Development and regenerative capacity of descending supraspinal pathways in tetrapods: a comparative approach. Adv Anat Embryol Cell Biol 145:1–145

ten Donkelaar HJ (2011) Motor systems. In: ten Donkelaar HJ (ed) Clinical neuroanatomy: brain circuitry and its disorders. Springer, Berlin/Heidelberg/New York, pp 367–447

ten Donkelaar HJ, Wesseling P, Semmekrot BA, Liem KD, Tuerlings J, Cruysberg JRM, de Wit PEJ (1999) Severe, non X-linked congenital miocrocephaly with absence of the pyramidal tracts in two siblings. Acta Neuropathol 98:203–211

ten Donkelaar HJ, Hoevenaars F, Wesseling P (2000) A case of Joubert's syndrome with extensive cerebral malformations. Clin Neuropathol 19:85–93

ten Donkelaar HJ, Willemsen MAAP, van der Heijden I, Beems T, Wesseling P (2002) A spinal intradural enterogenous cyst with well-differentiated muscularis propria. Acta Neuropathol 104:538–542

ten Donkelaar HJ, Lammens M, Wesseling P, Hori A, Keyser A, Rotteveel J (2004) Development and malformations of the human pyramidal tract. J Neurol 251:1429–1442

ten Donkelaar HJ, Lohman AHM, Keyser A, van der Vliet AM (2007) Het centrale zenuwstelsel. In: ten Donkelaar HJ, Lohman AHM, Moorman AFM (eds) Klinische Anatomie en Embryologie, 3rd edn. Elsevier, Maarssen, pp 981–1141 (in Dutch)

ten Donkelaar HJ, Keyser A, van Domburg P (2011) The somatosensory system. In: ten Donkelaar HJ (ed) Clinical neuroanatomy: brain circuitry and its disorders. Springer, Berlin/Heidelberg/New York, pp 133–209

Terashima T (1995a) Anatomy, development and lesion-induced plasticity of rodent corticospinal tract. Neurosci Res 22:139–161

Terashima T (1995b) Course and collaterals of corticospinal fibers arising from the sensorimotor cortex in the reeler mouse. Dev Neurosci 17:8–19

Terashima T, Inoue K, Inoue Y, Mikoshiba K, Tsukada Y (1983) Distribution and morphology of corticospinal tract neurons in reeler mouse cortex by the retrograde HRP method. J Comp Neurol 218:314–326

Theiler K (1988) Vertebral malformations. Adv Anat Embryol Cell Biol 112:1–99

Tohyama L, Lee VM-Y, Rorke LB, Trojanowski JQ (1991) Molecular milestones that signal axonal maturation and the commitment of human spinal cord precursor cells to the neuronal or glial phenotype in development. J Comp Neurol 310:285–299

Töndury G (1958) Entwicklungsgeschichte und Fehlbildungen der Wirbelsäule. Hippokrates, Stuttgart

Tsuchida T, Ensini M, Morton SB, Baldassare M, Edlund T, Jessell TM, Pfaff SL (1994) Topographic organization of embryonic motor neurons defined by expression of LIM homeobox genes. Cell 79:957–970

Tumpenny PD, Altman B, Cornier AS, Giampietro PF, Offiah A, Tassy O et al (2007) Abnormal vertebral segmentation and the notch signalling pathway in man. Dev Dyn 236:1456–1474

van der Knaap MS, Valk J (1995) Magnetic resonance of myelin, myelination and myelin disorders, 2nd edn. Springer, Berlin/Heidelberg/New York

Vaughn JE, Sims T, Nakashima M (1977) A comparison of the early development of axodendritic and axosomatic synapses upon embryonic mouse spinal motor neurons. J Comp Neurol 175:79–100

Veeneklaas GMH (1952) Pathogenesis of intrathoracic gastrogenic cysts. Am J Dis Child 83:500–507

Verbout AJ (1985) The development of the vertebral column. Adv Anat Embryol Cell Biol 90:1–122