Development and Developmental Disorders of the Spinal Cord

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6.1 Introduction

Even after its development is complete, the spinal cord remains a rather simple structure with a ventral, motor horn, a dorsal, sensory horn and an intermediate zone in between. Rexed (1952, 1954) introduced a subdivision of the spinal grey matter of the cat into ten layers, laminae I-X. His subdivision is now widely used (for human data see Schoenen and Faull 1990). The dorsal and ventral roots divide the spinal white matter into posterior (dorsal), lateral and anterior (ventral) funiculi. Classic birthdating studies by Altman and Bayer (1984) have demonstrated a ventral-to-dorsal gradient of histogenesis in the spinal cord with motoneurons appearing first, followed by neurons in the intermediate zone and, finally, neurons in the dorsal horn. More recent studies have unraveled many of the molecular mechanisms that specify cell fates in the spinal cord (reviewed in Lee and Jessell 1999; Jessell 2000; Briscoe and Ericson 2001; Caspary and Anderson 2003; Price and Briscoe 2004; Dalla Torre di Sanguinetto et al. 2008). A number of homeodomain and basic helix-loop-helix containing transcription factors has been identified that are expressed in the spinal ventricular zone in specific dorsoventral domains. In the spinal

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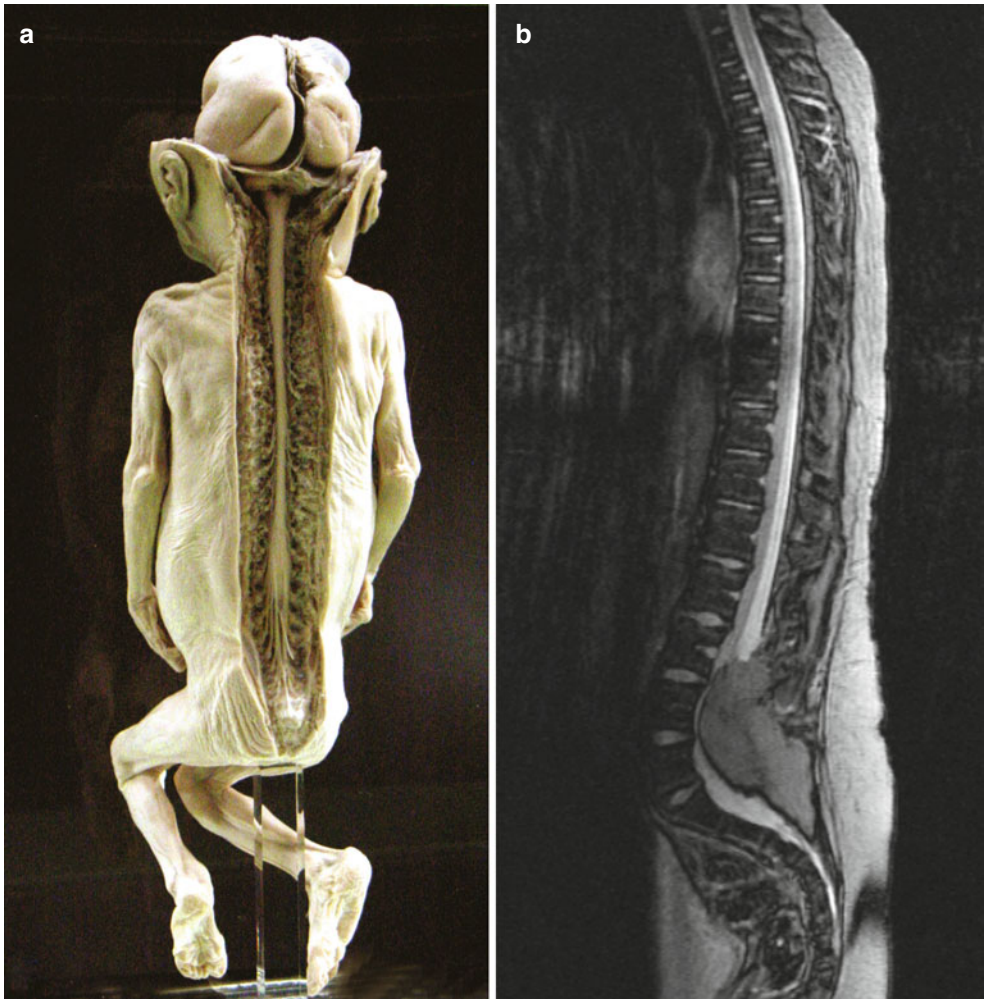

Fig. 6.1 (**a**) Dorsal view of the spinal cord in a 5-month-old fetus; (**b**) MRI of a tethered spinal cord in a newborn, due to a spinal lipoma (**a** from the Collection of the Anatomical Museum Nijmegen; kindly provided by Jos Dederen, Nijmegen; **b** kindly provided by Ton van der Vliet, Nijmegen)

cord, the sequential production of motor, relay and interneuron populations is parallelled by the appearance of descending supraspinal, propriospinal and ascending spinal projections around the same time with dorsal root fibres clearly lagging behind. The most frequent developmental disorders of the spinal cord are due to neural tube defects (Chap. 4), but other malformations may also result in developmental anomalies of the spinal cord, such as duplication of the cord, displacement of the cord by neurenteric cysts, syringomyelia and abnormal course or even absence of main fibre tracts.

In this chapter developmental events of spinal neuronal populations, the specification of spinal cell fates, the development of dorsal root, spinal ascending and descending supraspinal projections, and developmental anomalies of the spinal cord other than neural tube defects will be discussed.

6.2 Gross Development of the Spinal Cord

The morphology of the spinal cord in a 5-month-old fetus is shown in Fig. 6.1a. Clearly visible are the cervical and lumbar enlargements, the cauda equina and the dorsal root ganglia. Early development of the human spinal cord is shown in Fig. 6.2. Bayer and Altman (2002) presented an atlas of the human spinal cord from the fourth gestational week to the fourth postnatal month. Since the first description by His (1886) four plates are distinguished in the developing spinal cord (Fig. 6.2). Lateral to the central canal a dorsal alar plate, giving rise to the neurons of the sensory dorsal horn, and a ventral basal plate, giving rise to the motoneurons of the ventral horn, are found separated by the sulcus limitans. The alar plates are united by a thin roof plate that caps the central canal, whereas the floor plate forms the base of the spinal cord. On the basis of their extensive autoradiographic data, Altman and Bayer (1984, 2001) introduced an intermediate plate, and suggested that the dorsal (alar) neuroepithelium of the spinal cord gives rise to the sensory neurons of the dorsal horn, the ventral (basal) neuroepithelium to the motoneurons, and the intermediate neuroepithelium to the interneurons of the intermediate zone. The dorsal root ganglion (DRG) cells are derived from the neural crest. Their axons form two branches, one towards the periphery, the other towards the alar plate. Except for the occipital region, where ganglia are missing, each spinal ganglion corresponds to one somite. The central branches of the DRG cells form the dorsal roots of the spinal nerves. The developing motoneurons form the ventral roots of the spinal nerves. Between the fifth and sixth weeks of

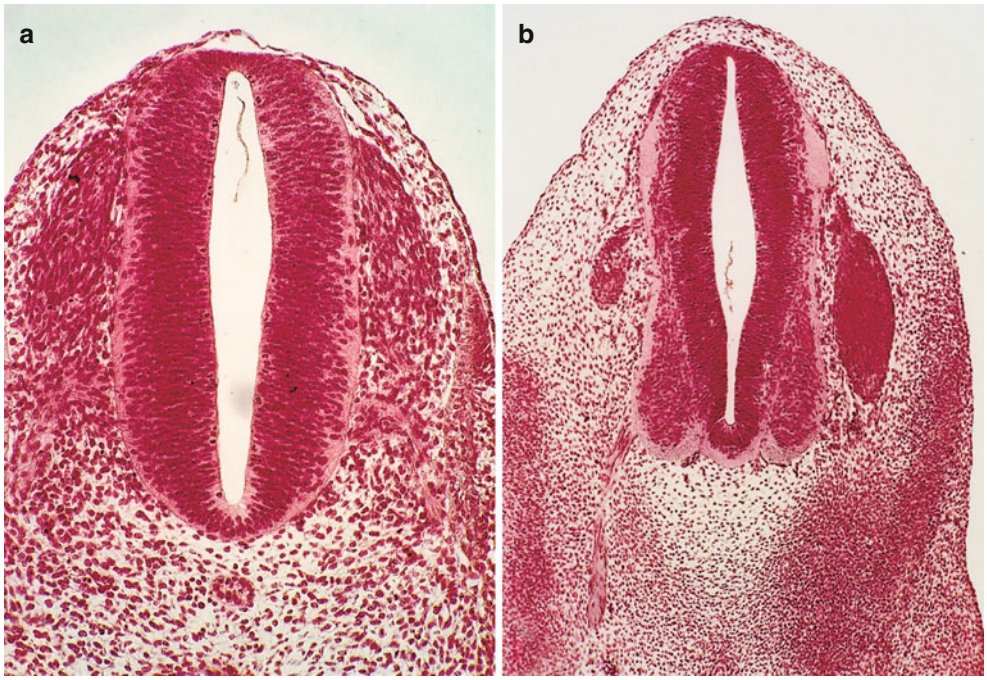

Fig. 6.2 Photomicrographs of the human spinal cord at Carnegie stages 13 (**a**) and 16 (**b**) (Taken from the Kyoto Collection of Human Embryos)

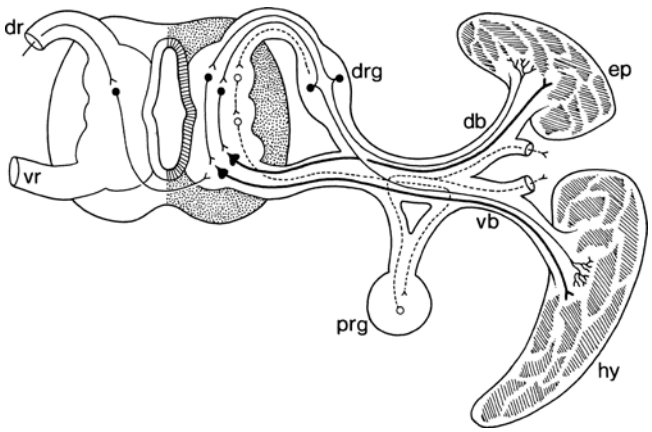

Fig. 6.3 Myotomal derivatives and their innervation. *db* dorsal branch, *dr* dorsal root, *drg* dorsal root ganglion, *ep* epimere, *hy* hypomere, *prg* paravertebral (sympathetic) ganglion, *vb* ventral branch, *vr* ventral root

development, a myotome becomes divided into a dorsal epaxial part or epimere and a ventrolateral hypaxial part, the hypomere (Fig. 6.3). The spinal nerves divide into dorsal rami for the dorsal musculature (mainly the erector spinae) and overlying skin, and ventral rami for the ventral musculature, including the muscles of the limbs, and the corresponding skin. Ventral rami at cervical and lumbosacral levels form the brachial and lumbosacral plexuses for the innervation of the limbs.

6.2.1 A Few Notes on the Development of the Vertebral Column

The vertebral column develops from the sclerotomes of the somites (Fig. 6.4). First, an unsegmented perichordal sheath is formed by cells spreading out from the sclerotomes. Second, loose, rostral and dense caudal areas form in a sclerotome. The loose zones of the sclerotomes are traversed by the intersegmental arteries and the spinal nerves. The dense parts form the neural arches of the vertebrae. Third, dense and loose zones also become evident in the cellular sheath of the notochord. The loose rostral zone forms the vertebral centrum, whereas the dense caudal zone becomes the intervertebral disc. Differential proliferation may be the main factor in establishing the alternating pattern of loosely and densely arranged mesenchymal zones (Rickenbacher et al. 1982; Verbout 1985; Christ 1990; O'Rahilly and Müller 2001). Finally, the neural processes will unite and close the neural arch. The sclerotomes from one pair of somites give rise to the caudal and cranial halves of two adjacent vertebrae. The formation of cartilage in the vertebral column begins at 6 postovulatory weeks and is far advanced at the end of the embryonic period (O'Rahilly and Meyer 1979). Ossification is detectable at about 9 weeks of development. In neonates, most vertebrae consist of cartilage with three ossification centres, one for the centrum and one for each half of the neural arch, giving a typical X-ray image. The transient occipitocervical region develops differently. Its four sclerotomes participate in the formation of the basioccipital unit of the skull base (Chap. 5).

Variations in number, form and position of vertebrae are rather common (Feller and Sternberg 1929; Töndury 1958; O'Rahilly et al. 1980, 1983, 1990a, b; Müller et al. 1986; Theiler 1988). Theiler (1988) studied the development of the vertebral column in 30 mutants of the laboratory mouse. Malformations of the vertebral column may be caused by disturbances of the somites, the notochord, and sclerotome differentiation. Recently, a role for Notch in abnormal vertebral

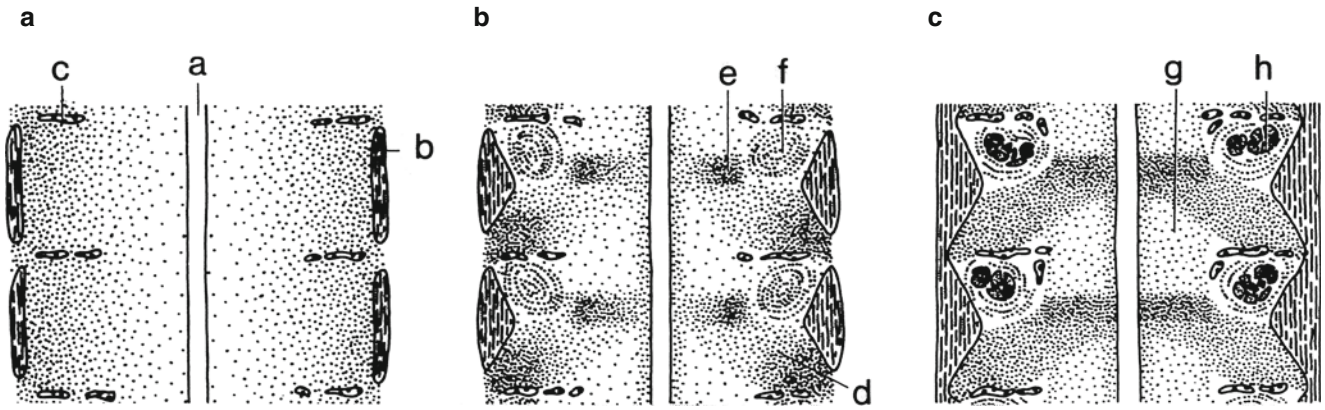

Fig. 6.4 The development of the vertebral column. (**a**) Around the notochord (*a*) non-segmentally arranged medial sclerotome mesenchyme is found, whereas more lateral parts of the sclerotome, close to the myotome (*b*), are more densely arranged and separated by segmental blood vessels (*c*). (**b**) The mesenchyme around the notochord is composed of alternating dense zones (*e*) from which the intervertebral discs arise, and looser zones from which the vertebral bodies arise. In the denser caudolateral parts of the sclerotomes (*d*) the vertebral arches and processes are formed, whereas in its less dense rostrolateral parts, the spinal nerves arise (*f*). (**c**) The contours of the vertebral bodies (*g*) and spinal nerves (*h*) are more clear (After Verbout 1985 and Christ 1990)

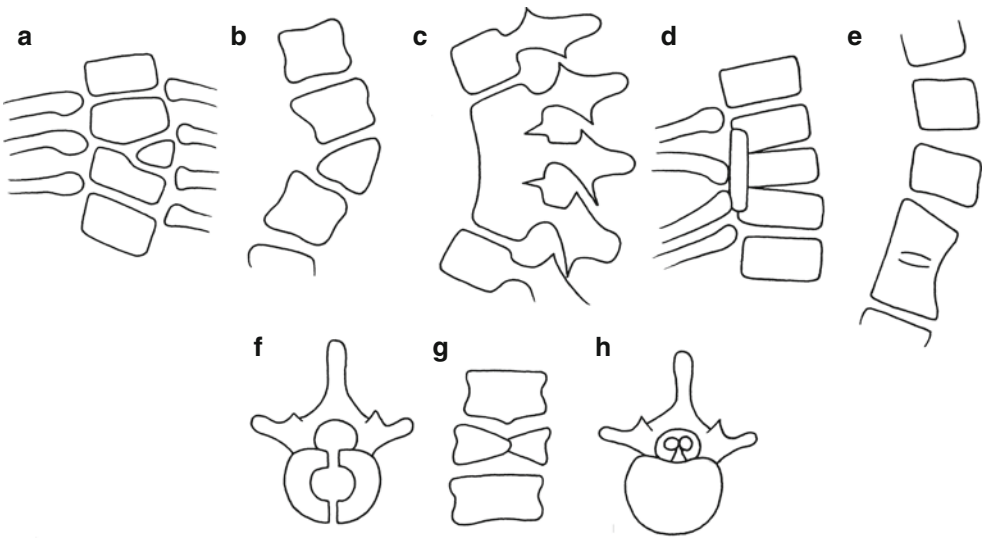

Fig. 6.5 Examples of vertebral anomalies that may affect the development of the spinal cord: (**a**, **b**) hemivertebrae; (**c**, **d**) bars; (**e**) block vertebra; (**f**) clefted vertebra; (**g**) 'butterfly' vertebra; (**h**) diastematomyelia (After O'Rahilly and Müller 2001)

segmentation has been demonstrated (Tumpenny et al. 2007; Dunwoodie 2009). Mutations in genes encoding Notch pathway components (*DLL3*, *MESP2*, *LFN9* and *HES7*) cause severe congenital vertebral defects. The majority of vertebral malformations such as fused and deformed vertebrae are caused by somite disturbances at early stages of development (in mice, embryos of 9–11 days). In the thoracic region, the combined appearance of deformed vertebrae and fused ribs is characteristic for somite disturbances. The human vertebral column usually consists of 24 presacral vertebrae. The last lumbar vertebra may be incorporated into the sacrum (***sacralization***), whereas the first sacral vertebra may be freed (***lumbarization***). Some ***vertebral anomalies*** are summarized in Fig. 6.5. Most common are spina bifida, hemivertebrae, block vertebrae and cleft vertebrae. In ***diastematomyelia***, a bony spur may lead to a duplication of the spinal cord (Sect. 6.8.2).

6.2.2 Ascensus Medullae

At the end of the embryonic period, the spinal cord still extends to the end of the vertebral column (Fig. 6.6). During the fetal period, it 'ascends' to lumbar levels owing to disproportional growth of the spinal cord and the vertebral column. Until the 11th gestational week the length of the spinal cord matches that of the vertebral column (Streeter 1919). Then, the 'ascensus' starts, the filum terminale is formed and the lower spinal nerves show a progressive obliquity caused by the shift between the spinal cord and the vertebral column. Collectively, the lower spinal roots form the cauda equina. In the newborn, the spinal cord ends at the level of the third lumbar vertebra, and in adults mostly at the level of the first or second lumbar vertebra. Developmental anomalies may lead to a tethered spinal cord (Fig. 6.1b). The tethered

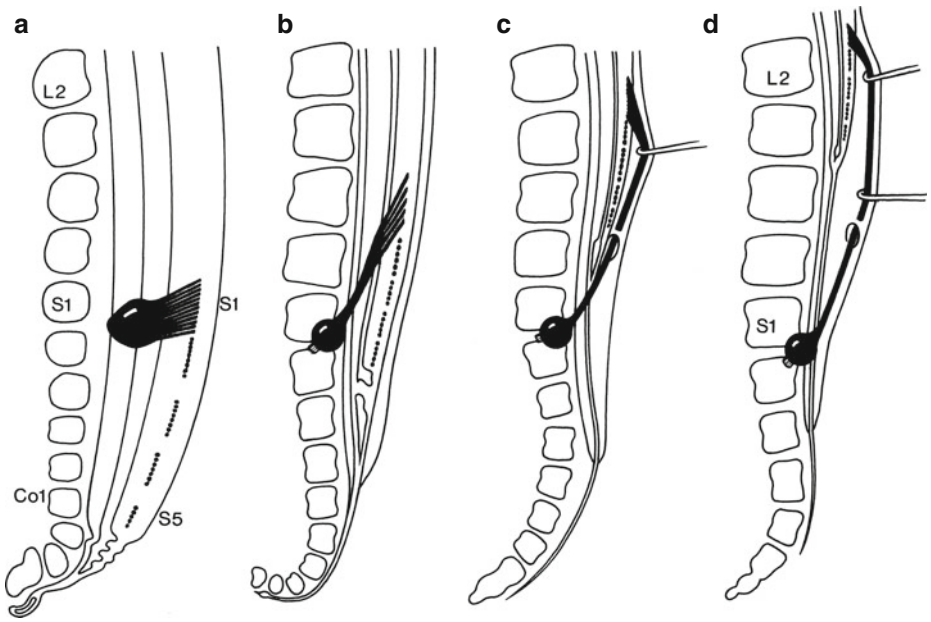

Fig. 6.6 'Ascensus medullae': (**a**–**d**) four successive stages in the development of the caudal end of the human spinal cord. They show the formation of the filum terminale and the progressive obliquity of the first sacral nerve (*S1*). *L2*, *S1* and *Co1* mark the second lumbar, first sacral and first coccygeal vertebrae (After Streeter 1919)

cord syndrome is usually reserved for lumbosacral defects in which there are variable combinations of thickening of the filum terminale, low or dilated conus medullaris, spinal lipoma, dermoid cyst, split cord, hydromyelia and sacral agenesis (Chap. 4). Clinical signs associated with cord tethering include lower limb motor and sensory deficits and neuropathic bladder. The severity of symptoms increases with age and patients are frequently treated surgically by untethering the spinal cord.

6.3 Developmental Events in Spinal Neuronal Populations

In rats, spinal neurons are generated in a sequential order from ventral to dorsal (Altman and Bayer 1984, 2001): first, the basal plate generates the motoneurons, followed by the intermediate plate that generates the relay neurons in the intermediate zone, and finally the alar plate produces the interneurons in the dorsal horn (Fig. 6.7, Table 6.1). Motoneurons are produced over a 2-day period: peak production is at E12 at cervical levels, and at E14 at thoracic and lumbar levels. The bulk of DRG cells are produced between E15 and E17. Large ganglion cells are generated before small ones. In general, contralaterally projecting interneurons appear to be generated earlier than the ipsilaterally projecting relay neurons (Nandi et al. 1993). The earliest dorsal root fibres enter the spinal cord at E13 at cervical levels (Altman and Bayer 1984). With carbocyanine dyes, Snider et al. (1992) traced the outgrowth of dendrites of cervical motoneuron pools and the development of dorsal root projections to these motor pools (Mirnics and Koerber 1995). At E15, the first day at which dorsal root fibres could be seen entering the cervical cord, the lateral motoneurons extend their dendrites medially or dorsomedially into the direction of the incoming dorsal root fibres. Between E15 and E17 dorsal root fascicles converge in the intermediate zone and fan out en route to the motor pools. Between E17 and E19 there is dense branching and bouton formation of muscle (Ia) afferents in the area of the motor pools.

Several types of interneurons can be distinguished in the spinal cord of rodents (Wentworth 1984b; Silos-Santiago and Snider 1992, 1994). In the rat thoracic cord, Silos-Santiago and Snider (1992) noted seven different types of commissural interneurons, i.e. interneurons with a contralaterally projecting axon, by E13.5. By E15, commissural interneurons were found near their final locations in the dorsal horn, the intermediate zone and the ventral horn. By E19, at least 18 different types of commissural interneurons were found. Also an increasing number of ipsilaterally projecting thoracic interneurons was found from E14 until E19 (Silos-Santiago and Snider 1994). Therefore, the rat embryonic spinal cord contains a large number of ipsilaterally projecting as well as commissural interneurons. In general, descending supraspinal, propriospinal and ascending spinal projections are formed around the same time, with dorsal root fibres clearly lagging behind. Spinal motoneurons first establish contacts with their target muscles, and subsequently are innervated by propriospinal fibres, descending supraspinal fibres and, finally, dorsal root collaterals.

In mice, motoneurons are generated at E10 and E11, neurons in the intermediate zone from E11 to E14, and dorsal horn neurons from E12 to E14 (Nornes and Carry 1978). Large DRG cells are generated in peak numbers at E10.5, whereas small DRG cells arise in greatest numbers at E12 (Sims and Vaughn 1979). The first axodendritic synaptic

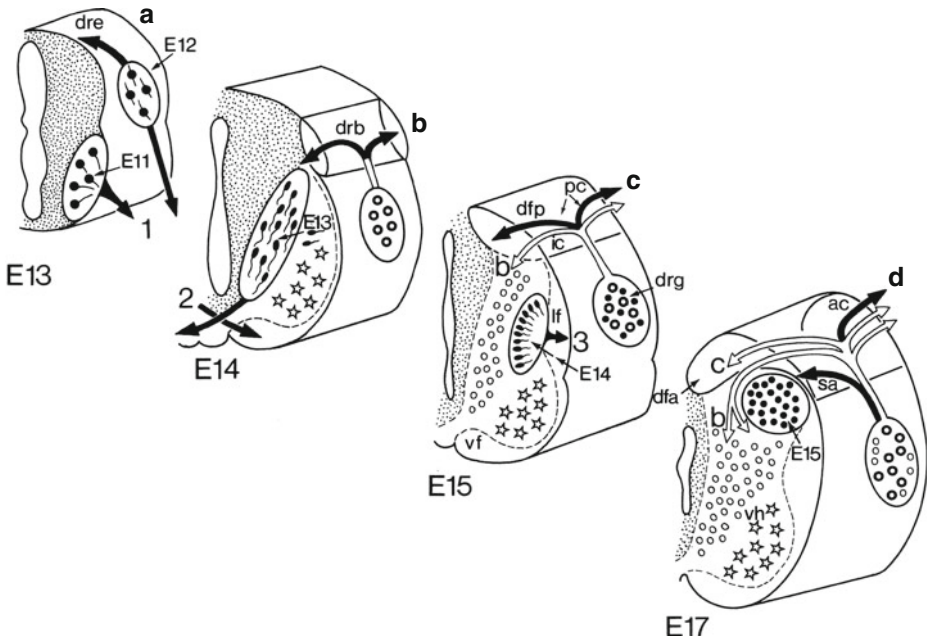

Fig. 6.7 Main developmental events in the rat cervical spinal cord from E13 until E17. At E13, onset of growth of peripheral motor fibres from the early-generated motoneurons (*E11*) and of sensory fibres from the early-generated dorsal root ganglion cells (*E12*) takes place (*1*). At E14, the ventral commissure and ventral funiculi are formed (*2*) by the axons of contralaterally projecting relay neurons that are generated at E13. At E15, lateral migration of the ipsilaterally projecting relay neurons (generated around E14) occurs (*3*), and interneurons in the dorsal horn and small dorsal root ganglion cells are generated. At E17, the dorsal funicular ascending zone is formed. (**a**–**d**) The ingrowth of dorsal root fibres: (**a**) arrival of the earliest dorsal root fibres at the dorsal root entrance zone (*dre*); (**b**) formation of the dorsal root bifurcation zone (*drb*); (**c**) formation of the dorsal funiculus propriospinal zone (*dfp*) by the ingrowing intersegmental dorsal root collaterals; (**d**) formation of the dorsal funicular ascending zone (*dfa*) by the growing suprasegmental dorsal root collaterals. *ac* ascending dorsal root collaterals, *ic* intrasegmental collaterals, *lf* lateral funiculus, *pc* propriospinal collaterals, *sa* small-caliber collaterals, *vf* ventral funiculus, *vh* ventral horn (After Altman and Bayer 1984)

Table 6.1 Time of neuron origin data in the rat spinal cord (after Altman and Bayer 1984) and estimated data for the human spinal cord (after Bayer et al. 1995; Altman and Bayer 2001)

Time of neuron origin	Rat	Man
Motoneurons		
Cervical cord	E11-E12	3.5–5.7 weeks of development
Thoracic cord	E12-E13	4.1–5.7 weeks of development
Lumbar cord	E12-E13	4.1–5.7 weeks of development
Intermediate zone	E13-E15	Fourth to fifth week
Dorsal horn (substantia gelatinosa)	E15-E16	6.7–7.4 weeks of development
Dorsal root ganglion cells	E12-E15	Fourth to fifth week
Ascending tract neurons		
Contralaterally projecting neurons	E12-E13	4.1–5.7 weeks of development
Ipsilaterally projecting neurons	E14	5.8–6.6 weeks of development

contacts on mouse lateral motoneurons, presumably propriospinal in origin, were found at E11 (Vaughn et al. 1977; Wentworth 1984a). Both axodendritic and axosomatic synapses were found at E12. Most of the early-forming, lateral motoneuronal dendrites grow into the lateral marginal zone, where they come into contact with axons of interneurons. The initial trajectories of sensory axons to the spinal cord were studied with carbocyanine tracing (Sect. 6.5). In the human spinal cord, neurons are generated in a similar sequential order as in rodents between the third and sixth weeks of development (Altman and Bayer 2001; Table 6.1).

6.4 The Specification of Cell Fates in the Spinal Cord

In general, neuronal subtypes in the ventral spinal cord, arising from the basal plate, regulate motor output, whereas neurons in the dorsal spinal cord, arising from the alar plate, mediate and integrate sensory input. The development of both sets of neurons is induced by extracellular signalling molecules, secreted by the notochord and the adjacent ectoderm. The Sonic hedgehog (SHH) protein of the *Sonic hedgehog* (*Shh*) gene in the notochord induces the formation of the floor plate (Jessell 2000; Placzek et al. 2000; Patten et al. 2003). In its turn, the floor plate induces the formation of motoneurons and ventral interneurons in the basal plate. Bone morphogenetic proteins from the ectoderm induce the formation of the alar and roof plates. These secreted factors act in opposing gradients to pattern the

spinal cord by acting on prepatterning homeodomain and proneural basic helix-loop-helix transcription factor genes (Fig. 6.8). Different sets of prepatterning and proneural genes are involved in the specification of ventral and dorsal spinal cell types (Lee and Jessell 1999; Briscoe and Ericson 2001; Sharma and Peng 2001; Caspary and Anderson 2003; Gómez-Skarmeta et al. 2003; Price and Briscoe 2004; Dalla Torre di Sanguinetto et al. 2008).

6.4.1 Specification of Neuronal Fates in the Ventral Spinal Cord

SHH from the notochord is required to pattern the ventral neural tube. Ectopic expression of SHH is capable of inducing ventral spinal cord cell types (Echelard et al. 1993; Roelink et al. 1994), whereas eliminating SHH function by antibody blockade or gene targeting prevents the differentiation of floor plate cells, motoneurons, ventral interneurons and oligodendrocytes (Marti et al. 1995; Chiang et al. 1996; Ericson et al. 1996, 1997; Orentas et al. 1999; Pierani et al. 1999; Litingtung and Chiang 2000; Ruiz i Altaba et al. 2003). The dorsalmost ventral interneurons do not depend on SHH signalling, but can be induced by a parallel, retinoid-mediated pathway (Pierani et al. 1999). In the ventral spinal cord, graded concentrations of SHH set up domains of gene expression along the ventrodorsal axis (Fig. 6.8). Progressively two- to threefold changes in SHH concentration generate five molecularly distinct classes of ventral neurons, the motoneurons and the V0, V1, V2 and V3 types of interneurons. Two classes of homeodomain proteins expressed by these ventral progenitor cells act as intermediary factors in the interpretation of the graded SHH signalling (Pierani et al. 1999; Briscoe et al. 2000; Briscoe and Ericson 2001; Ruiz i Altaba et al. 2003). The expression of each class I protein (Dbx1, Dbx2, Irx3, Pax6 and Pax7) is repressed at a distinct SHH concentration, so that their ventral boundaries of expression delineate progenitor domains. In contrast, the expression of each class II protein (Nkx2.2, Nkx6.1, Nkx6.2 and Olig2) requires SHH signalling and is achieved at a

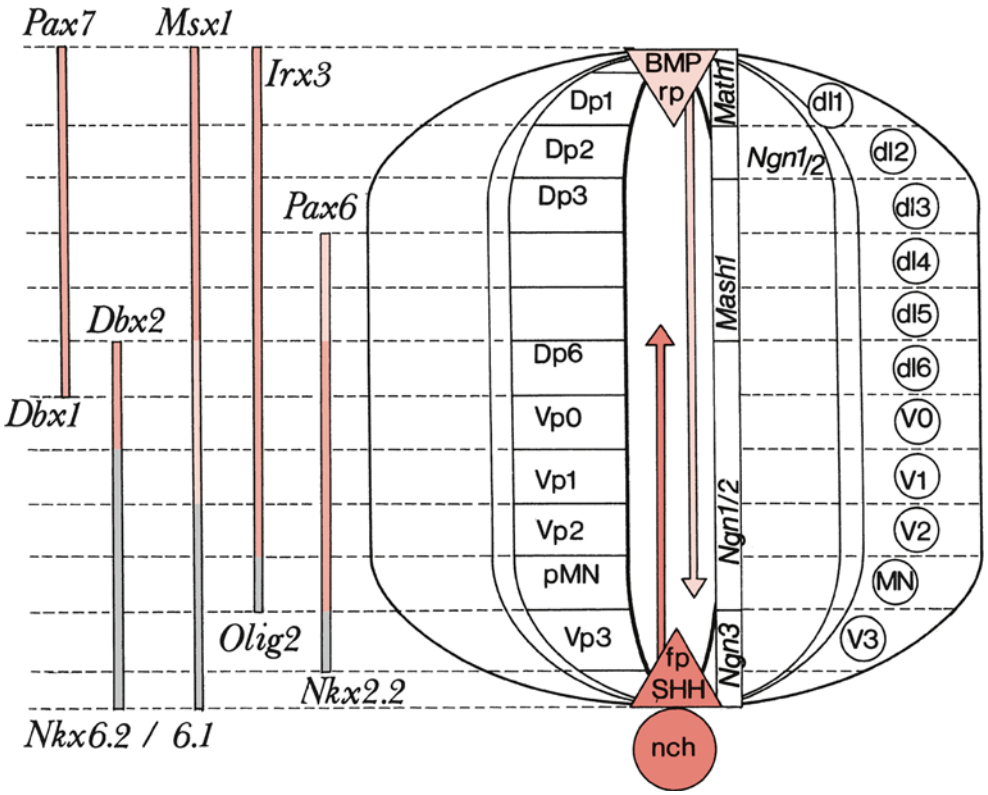

Fig. 6.8 Expression patterns of secreted factors, proneural and dorsoventral prepatterning genes in the vertebrate spinal cord. The secreted factors Sonic hedgehog (*SHH*) from the notochord (*nch*) and the floor plate (*fp*) and bone morphogenetic proteins (*BMP*) from the roof plate (*rp*) act in opposing gradients to pattern the spinal cord by acting on prepattern (at the *left*) and proneural (indicated within the spinal cord) genes in different dorsal/ventral territories. The prepatterning genes *Nkx2.2*, *Nkx6.1* and *Nkx6.2* are expressed in ventral-to-dorsal domains. *Olig2* is expressed in a ventral domain within the *Nkx6.1* territory. *Msx1*, *Pax7*, *Irx3* and *Pax6* are expressed in dorsal-to-ventral domains. *Dbx1* and *Dbx2* are expressed in intermediate territories. The combinatioral code of these factors specifies different progenitor domains (*Dp1-Dp6*, *Vp0-Vp3* and *pMN*), in which the corresponding neurons (*dI1-dI6*, dorsal interneurons, *V0-V3*, ventral interneurons *MN* motoneurons) are specified. The proneural gene *Math1* is expressed in a dorsal domain that is complementary to a dorsal domain that expresses *Ngn1* and *Ngn2*. *Mash1* is expressed in an intermediate territory that separates the dorsal and ventral domains of *Ngn1/2*. *Ngn3* is expressed adjacent to the floor plate (After Diez del Corral and Storey 2001; Marti and Bovolenta 2002; Gómez-Skarmeta et al. 2003)

distinct SHH concentration, so that their dorsal boundaries delineate progenitor domains. Postmitotic motoneurons are marked by the expression of *Isl1*/*Isl2* and *Hb9*, whereas the postmitotic ventral interneurons express the *Evx1*/*Evx2*, *En1*, *Chx10*/*Lhx3* and *Sim1* transcription factor genes, respectively (Burrill et al. 1997; Ericson et al. 1997; Matise and Joyner 1997; Arber et al. 1999; Pierani et al. 1999; Briscoe et al. 2000). The initial generation of several neuronal subtypes is only the beginning of the assembly of functional spinal circuits, motor as well as sensory. Spinal motoneurons are further divided into longitudinally organized medial and lateral columns and, subsequently, motoneurons innervating particular muscles are grouped into motor pools. The segregation of spinal motoneurons is correlated with the expression of LIM-homeodomain proteins (Tsuchida et al. 1994; Pfaff and Kintner 1998; Kania et al. 2000). Neurons of the medial part of the medial motor column, innervating dorsal axial muscles such as the erector spinae, coexpress *Isl1*, *Isl2* and *Lim3*, whereas neurons of the lateral part of the medial motor column, innervating ventral axial muscles (ventral body wall muscles), coexpress *Isl1* and *Isl2* only (Fig. 6.9). In a similar way, two parts of the lateral motoneuron column can be characterized by the coexpression of *Isl1* and *Isl2* (a medial part innervating ventral limb muscles) and *Isl2* and *Lim1* (a lateral part innervating dorsal limb muscles), respectively. Examples of the organization of chick motor pools and zebrafish primary motoneurons are shown in Fig. 6.10.

The fate of the various classes of ventral interneurons is only beginning to be unraveled. V1 interneurons appear to be short propriospinal neurons, terminating one to two segments rostrally, close to motoneurons (Saueressig et al. 1999). Possibly, these interneurons represent Renshaw or Ia-inhibiting interneurons (Wenner et al. 1998; Wenner and O'Donovan 1999). V0 interneurons are commissural interneurons (CINs) that project locally over one to four spinal segments (Moran-Rivard et al. 2001; Pierani et al. 2001; Lanuza et al. 2004). Throughout vertebrates, certain ventral interneurons are involved in neural networks or central pattern generators that generate the basic motor patterns underlying rhythmic limb movements.

The neuronal components of the **central pattern generators** (**CPGs**) integrate three key functions (Grillner 2003; Kiehn and Butt 2003; Grillner and Jessell 2009; Kiehn 2011): the generation of a stable rhythm, the ipsilateral coordination of flexors and extensors, and bilateral coordination over the midline. Both excitatory and inhibitory CINs contribute to the coordination of left-right activities during locomotion (Fig. 6.11). V0 interneurons predominantly form inhibitory CINs and play a role in securing left-right alternation (Lanuza et al. 2004). The predominantly excitatory V3 interneurons participate in the establishment of a regular and balanced motor rhythm distributing drive over the midline (Zhang et al. 2008). Studies of *Netrin-1* knockout mice confirmed that the V3 population is an important component of

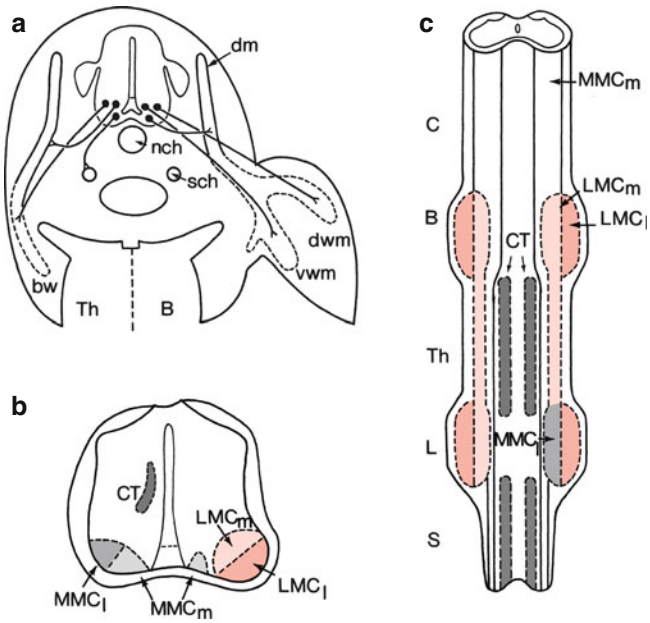

Fig. 6.9 LIM codes in chick spinal motoneurons. A cross section of a E3.5-chick embryo (**a**), a section through the spinal cord of an E8 embryo (**b**) and a ventral view of the spinal cord at E8.5 (**c**). At first (**a**), motoneuron subtypes are intermixed but have distinct pathways in the periphery. Neurons of the medial part of the medial motor column (MMC_m, *light grey*) coexpress *Isl1*, *Isl2* and *Lim3* and their axons grow towards the dorsal myotome (*dm*). Neurons of the lateral part of the medial motor column (MMC_l, *dark grey*) coexpress *Isl1* and *Isl2* and grow towards the ventral body wall muscles (*bw*). Axons of neurons of the medial part of the lateral motor column (LMC_m, *light red*) also coexpress *Isl1* and *Isl2* and supply the ventral premuscle mass of the wing (*vwm*). Neurons of the lateral part of the lateral motor column (LMC_l, *red*) coexpress *Isl2* and *Lim1* and innervate the dorsal premuscle mass (*dwm*). Preganglionic sympathetic neurons of the column of Terni (*CT*, *black*) express *Isl1* and innervate the paravertebral sympathetic chain (*sch*). Later (**b**, **c**), the five motoneuron subtypes, distinguished by their individual *LIM*-homeobox gene codes, have segregated into columns. *C*, *B*, *Th*, *L* and *S* indicate cervical, brachial, thoracic, lumbar and sacral parts of the spinal cord (After data by Tsuchida et al. 1994)

the left-right synchrony circuitry (Rabe et al. 2009). Netrin-1 and its receptor DCC play an important role in axon pathfinding and migration of spinal neurons (Chap. 2). *Netrin-1* deletion leads to a loss of CINs resulting in strict left-right synchrony during fictive locomotion (Rabe et al. 2009). Moreover, mice carrying a null mutation of *DCC* showed an uncoordinated left-right activity during fictive locomotion accompanied by a loss of interneuronal subpopulations originating from commissural progenitors (Rabe Bernhardt et al. 2012). The ephrin receptor A4 (EphA4) and its ephrin ligand B3 (ephrin-B3) also play a role in CPGs (Kiehn and Butt 2003; Grillner and Jessell 2009; Kiehn 2011). In *EphA4* knockout mice, the normal alternating walking pattern is replaced by a rabbit-like hopping gait (Restrepo et al. 2011). This hopping gait may be explained by the abnormal midline crossing of ipsilateral axons and is the result of a change in the balance between excitatory and inhibitory signals across the midline. *EphA4* mutants had increased numbers of CINs

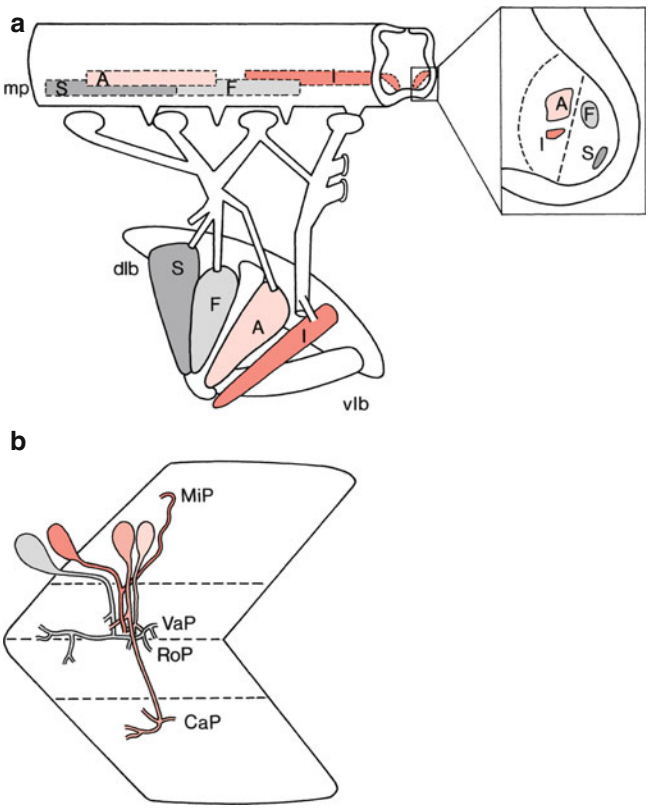

Fig. 6.10 Organization of motor pools in the chick hindlimb (**a**) and primary motoneurons (**b**) in the zebrafish. (**a**) Motor pools (*mp*) of the sartorius (*S*), femorotibialis (*F*), adductor (*A*) and ischioflexor (*I*) muscles and their targets are shown in different colours. (**b**) Primary 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)

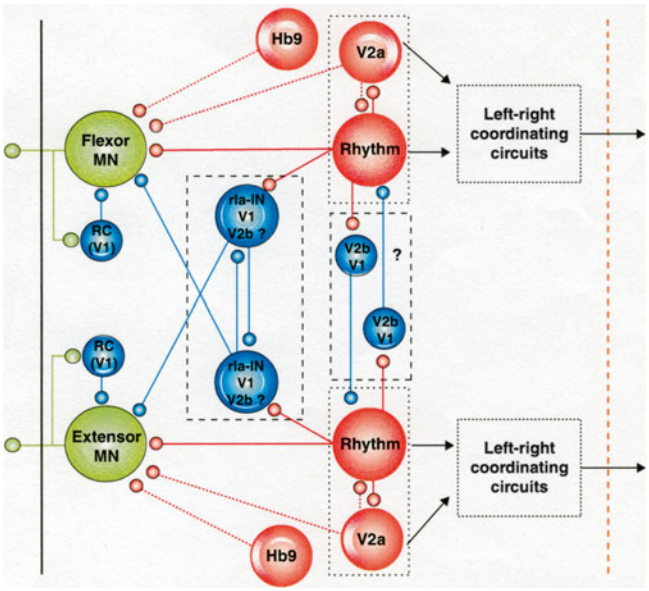

Fig. 6.11 Diagram of the rodent CPG. Flexor and extensor motoneurons (*MNs*) are driven to rhythmicity by alternating excitation and inhibition. Excitatory rhythm-generating neurons, therefore, need to drive premotor inhibitory neurons. Candidate premotor inhibitory neurons are Ia-interneurons connected 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).

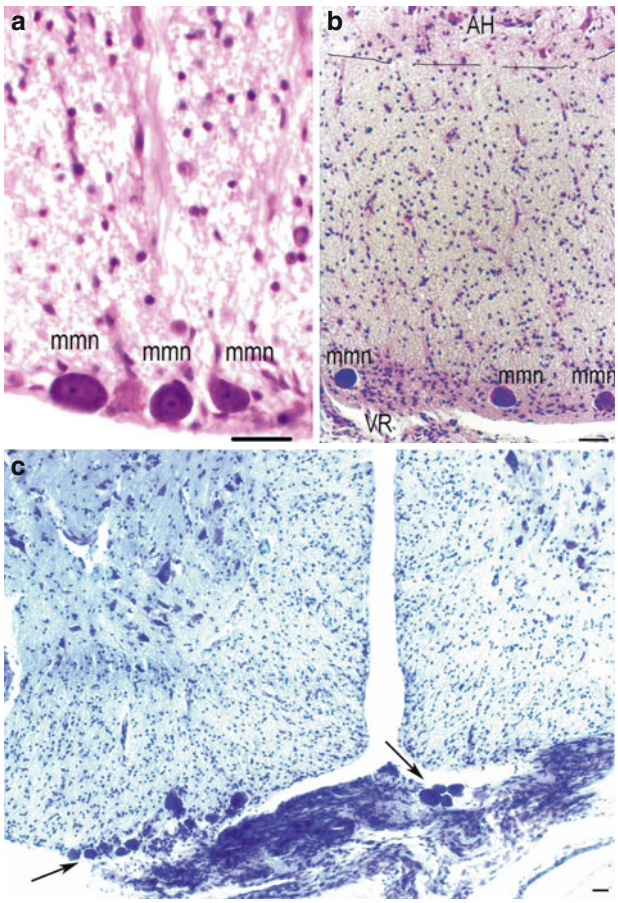

Fig. 6.12 Accumulation of heterotopic (migratory) motoneurons (*mmn*) at the anterior rim of the spinal cord in: (**a**) a female 5-month-old SMA-I subject, (**b**) a male 8-month-old SMA-I subject, and (**c**) in some sections, particularly those of younger SMA-I subjects, more than ten heterotopic 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)

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Clinical Case 6.2. Hypoplasia of the Spinal Cord in a Case of Lethal Congenital Contracture Syndrome

The ***lethal congenital contracture syndrome*** (***LCCS***) is an autosomal disorder, characterized by the fetal akinesia phenotype, multiple contractures of joints and degeneration of spinal motoneurons (Herva et al. 1988; Vuopala et al. 1995; Pakkasjärvi et al. 2006). This primarily Finnish disorder is caused by mutations in *GLE1*, a protein required for transport of mRNA from nucleus to cytoplasm (Nousiainen et al. 2008). Recently, Itoh et al. (2013) presented a Japanese case (see Case Report).

Case report. A female fetus showed akinesia and contractures of the joints of the upper and lower limbs at fetal ultrasonography at 12 weeks of gestation, and was stillborn at 21 weeks and 3 days of gestation with a birth weight of 230 g (353 ± 125 g). The family history was unremarkable. The baby showed several contracture deformities, including hyperflexion of both elbows, camptodactyly, hyperflexion of knees and ankles, a dislocated hip joint, rocker-bottom feet, but no pterygia (Fig. 6.13a). The ribs were very thin (Fig. 6.13b). The size

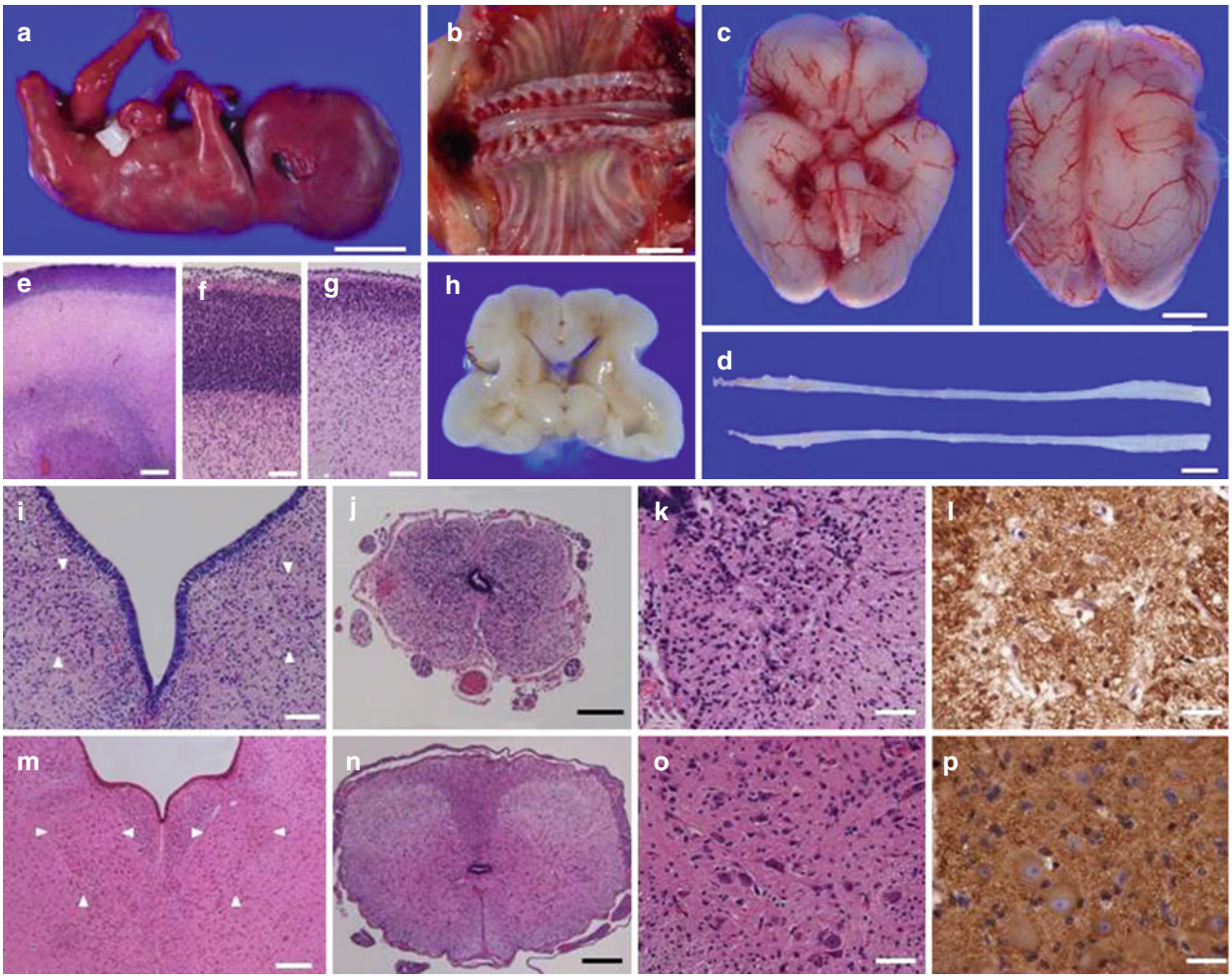

Fig. 6.13 Macroscopic and microscopic features of a lethal congenital contracture syndrome: (**a**) multiple arthrogryposis with hyperflexion of the elbows, knees and elbows, a dislocated hip joint and rocker-bottom feet; (**b**) very thin ribs; (**c**) the cerebral hemispheres with a premature dip of the Rolandic sulci; (**d**) an extremely thin spinal cord; (**e**, **f**) normally formed cerebral cortex; (**g**) normal cerebellar cortex; h coronal, unstained section of the cerebrum, showing a normal cerebral cortex, basal ganglia and thalamus; (**i**, **m**) a hypoplastic hypoglossal nucleus with poorly differentiated motoneurons (**i**) as compared to that of an age-matched control (**m**); (**j**, **k**, **n**–**p**) thoracic cord of the present case (**j**, **k**) compared to that of an age-matched control (**n**–**p**); motoneurons were decreased in number and showed immature features; some motoneurons showed loss of β-III tubulin-immunoreactivity (**l**). The sections were stained for hematoxylin-eosin or for β-III tubulin-immunoreactivity (**l**, **p**). *Scale bars* = 3 cm (**a**), 1 cm (**b**–**d**, **h**), 500 μm (**e**), 250 μm (**j**, **n**), 100 μm (**f**, **g**, **i**, **m**), 50 μm (**h**, **k**, **o**) or 25 μm (**l**, **p**) (From Itoh et al. (2013; the photomicrographs were kindly provided by Kyoko Itoh, Kyoto))

of the brain was, except for the cerebellum and the spinal cord, normal for the gestational age. The cerebral hemispheres showed a premature dip of the Rolandic sulci (Fig. 6.13c, d). The cerebral cortex was histologically normal and composed of the cortical plate, the subplate and intermediate, subventricular and ventricular zones (Fig. 6.13e, f). The spinal cord was extremely thin from the cervical to the sacral level (Fig. 6.13d). The cerebellar hemispheres (Fig. 6.13g) and the caudal medulla were also small. The spinal cord was small throughout its length with thin ventral and dorsal roots (Fig. 6.13i). Premature motoneurons were observed in the ventral horn, but fewer in number than normal with a reduced cell size and poor immunoreactivity for β-III tubulin (Fig. 6.13k, l). The dorsal horn and the ventral and lateral funiculi were normally developed, but the dorsal funiculus was poorly developed. In the caudal medulla, the hypoglossal and ambiguus nuclei were hypoplastic with poorly differentiated motoneurons (Fig. 6.13i). The muscle fibres of the iliopsoas muscle and the diaphragm showed group atrophy with a large number of round and small muscle fibres.

The genetic analysis of *GLE1* revealed a heterozygous mutation of A841G (Ile243Val). However, it is not clear whether or not the A841G mutation was responsible for the phenotype seen in the present case. The differential diagnosis of this case includes LCCS, LAAHD (lethal arthrogryposis with anterior horn cell disease) and Pena-Shokeir syndrome (Hall 2009). Although no definitive mutation in the *GLE1* gene was found, other molecules interacting with *GLE1* may be responsible for the hypoplastic motoneurons in the spinal cord and caudal medulla.

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).

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6.4.2 Patterning Cell Types in the Dorsal Spinal Cord

For the proper development of interneurons in the dorsal spinal cord a different set of genes must be expressed (Lee and Jessell 1999; Matise 2002; Caspary and Anderson 2003; Marmigere and Ernfors 2007). In mice, four non-overlapping expression domains of proneural genes define six progenitor types in the dorsal spinal cord at E10 (Gowan et al. 2001). These differentiate into six types of dorsal interneurons (dI1-dI6; Fig. 6.8) which can be characterized by E10 on the basis of the repertoire of the homeodomain transcription factors that they express (Gross et al. 2002; Müller et al. 2002). Proneural genes appear to be required between E9.5 and E12 to initiate the development of distinct neuronal classes. *Math1* is expressed in the dorsalmost cells adjacent to the roof plate (dI1), *neurogenin 1* (*Ngn1*) and *Ngn2* are expressed in domains of the adjacent ventral band of cells (dI2) and *Mash1* is expressed by the progenitors that will become dI3-dI5. *Ngn2* and *Ngn1* are also expressed by the first and second waves of migratory neural crest cells that form DRG cells (Ma et al. 1999; Reed-Geagham and Maricich 2011). The dorsal interneuron subtypes 1–3 (dI1-dI3 cells) migrate ventrally, and the dI4 and a subset of dI5 cells migrate laterally to populate the deep layers of the dorsal horn (laminae IV-V). Another subset of dI5 cells and the dI6 interneurons migrate towards the ventral horn. Three additional populations of interneurons are born later, beginning at E12. Late-born cells, expressing the proneural gene *Math1* and the LIM-homeodomain transcription factor gene *Lhx2a*, settle deep in the dorsal horn near earlier born *Math1*-expressing interneurons. Both cell types may be involved in proprioception. Two other late-born populations derive from dI4 and dI5 cells, and they express either *Pax2* and *Lim1/2*, or *Lmx1b* alone. These cells migrate to the superficial layers of the dorsal horn, where they may mediate pain and temperature. So far, the best understood dorsal interneurons are the dI1 cells which express *Math1*. *Math1*-mutant mice lack dI1 cells (Bermingham et al. 2001; Gowan et al. 2001). The mutants have fewer cells in the population of ventrally projecting commissural neurons, and they show a clear loss of fibres in the spinocerebellar tracts (Arber et al. 2000). DI2 cells are still present in *Math1*-mutant mice as well as in *Ngn1* mutants, but not in *Ngn1/Ngn2*

double-mutant animals (Ma et al. 1999). These mutants lack all dl2 interneurons, and have fewer ventrally projecting commissural neurons, indicating that dl2 cells contribute to this population of propriospinal neurons. The aforementioned data suggest that interneurons derived from *Mash1*-expressing progenitors contribute to both deep and superficial layers of the dorsal horn, whereas *Math1*-expressing cells migrate exclusively to the deep laminae (Caspary and Anderson 2003).

6.5 Development of Dorsal Root Projections

Afferent (sensory) fibres from cutaneous, muscle and joint receptors innervate the spinal cord. After entering the spinal cord, the dorsal root fibres divide into ascending and descending branches. These branches give off collaterals to the dorsal horn. The ascending branches of the thicker fibres reach the dorsal column nuclei in the medulla. The dorsal root fibres vary in thickness. The thickest myelinated fibres (Aα, from muscle spindles and tendon organs) end in the deeper layers of the dorsal horn and partly in the ventral horn (Fig. 6.14). Thick, myelinated fibres from cutaneous receptors (Aβ) end in laminae III-VI of Rexed (Willis and Coggeshall 1991). The thinnest myelinated and unmyelinated dorsal root fibres (Aδ and C), largely from nociceptors, end in laminae I and II and parts of lamina V. With carbocyanine tracers (Fig. 6.15), Snider and co-workers (Snider et al. 1992; Ozaki and Snider 1997) studied the development of the interactions between dorsal root fibres and their targets in the spinal cord of rodents (Kudo and Yamada 1987). In the developing rat spinal cord, Ia axons project towards spinal motoneuron pools in fascicles that exhibit a considerable degree of spatial order. Although motoneuron dendritic projections are well established, the dendrites projecting directly into the path of incoming Ia afferents appear not to guide afferents to appropriate motor pools. The Ia afferents pass over the distal dendrites and grow all the way to the border between grey and developing white matter. Terminal branching and formation of boutons are found in the vicinity of motoneuron somata and proximal dendrites, but hardly on distal dendrites. In mice, Ozaki and Snider (1997) studied the initial trajectories of sensory axons to the thoracic spinal cord. Primary afferent axons reach the thoracic cord at E10.5, and grow rostrocaudally for at least 48 h prior to extending collateral branches into the grey matter. After this 'waiting period', different classes of murine primary afferent fibres enter the spinal cord in sequence: muscle afferents penetrate the grey matter as early as E13.5, large-caliber sensory afferents first penetrate at E14.5, and most fine cutaneous afferents enter at E15.5. These different classes of sensory axons terminate in different layers of the spinal cord. Apparently,

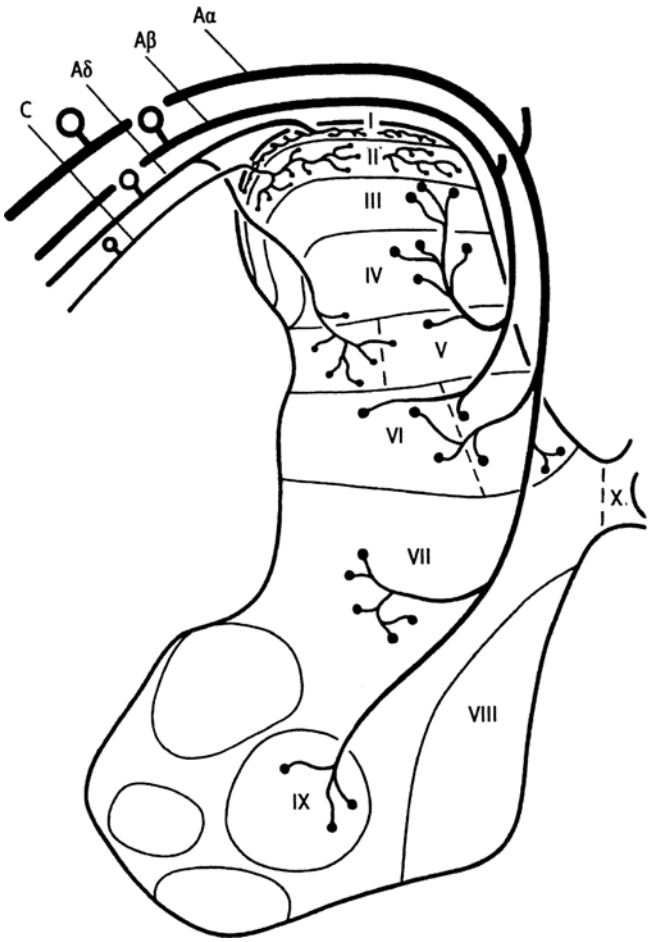

Fig. 6.14 The laminar terminations of dorsal root projections. The thickest myelinated fibres (*Aα*, from muscle spindles and tendon organs) end in the deep parts of the dorsal horn and partly in the ventral horn. Thick, myelinated fibres from cutaneous mechanoreceptors (*Aβ*) end in laminae *III-VI*. The thinnest myelinated (*Aδ*) and unmyelinated (*C*) dorsal root fibres, largely from nociceptors, end in lamina *I* and *II* and in parts of lamina *V* (After Brodal 1992)

these projections are precise from the entrance of the spinal cord (Ozaki and Snider 1997), and axons are probably guided by intraspinal cues such as the neurotrophin NT-3 and semaphorin-D (Sharma and Frank 1998; Sanes and Yamagata 1999).

In the spinal cord of pyridine silver stained human embryos of 5–8 weeks of estimated menstrual age, i.e. about 3–6 postovulatory weeks, Windle and Fitzgerald (1937) studied the development of dorsal root projections. At approximately E27 (about Carnegie stage 13/14), DRG cells and motoneurons are present (Fig. 6.16). Central processes of the bipolar ganglion cells reach the spinal cord, where they initiate the formation of the dorsal funiculi. At first, the dorsal funiculi are found only in the cervical spinal cord, and are composed of short fibres, but by stage 15 dorsal funiculi are found throughout most of the spinal cord. At stage 18, collateral branches of primary afferent fibres

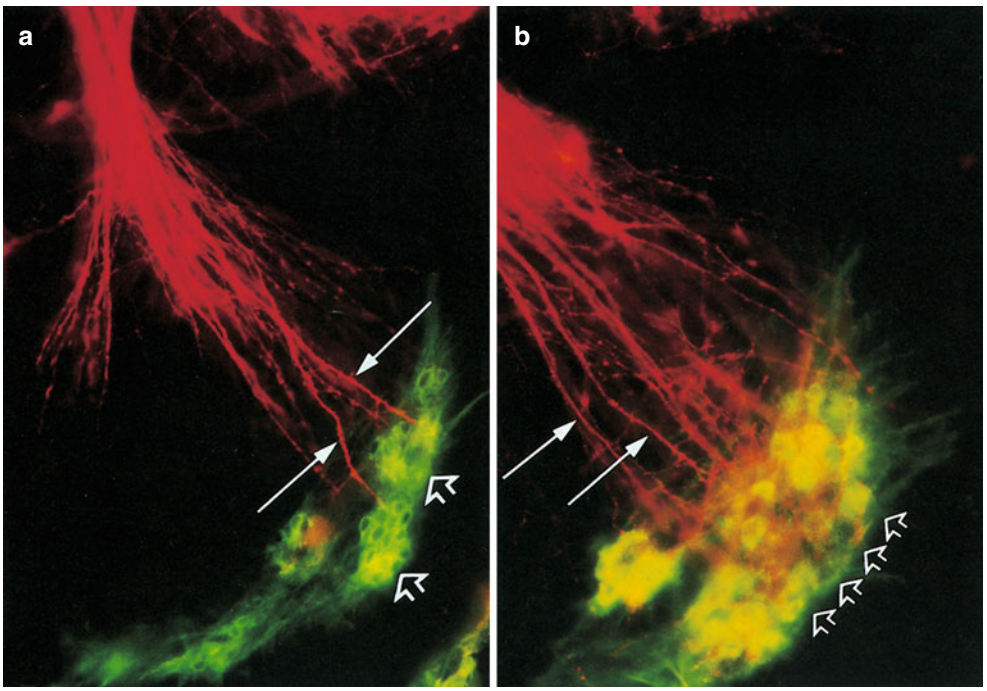

Fig. 6.15 Development of dorsal root projections as found by carbocyanine labelling in rat embryos. Ia-afferent fibres were stained with 1,1′-dioctadecyl–3,3,3′,3′- tetramethylindocarbocyanine perchlorate (*DiI*) and motoneurons with 4,4–dihexadecyl aminostyryl–*N*–methylpyridinium iodide (*DiA*). At E17 (**a**), Ia fascicles (*long arrows*) have reached motoneuron somata (*open arrows*). At P2 (**b**), predominantly unbranched Ia fascicles (*long arrows*) reach the motoneuron pool. Terminal branching (*orange*) is on motoneuron somata. *Open arrows* indicate the border between motoneurons and the developing funiculi (Reproduced with permission from Snider et al. 1992; copyright 1992, Wiley-Liss Inc, a subsidiary of John Wiley & Sons, Inc.)

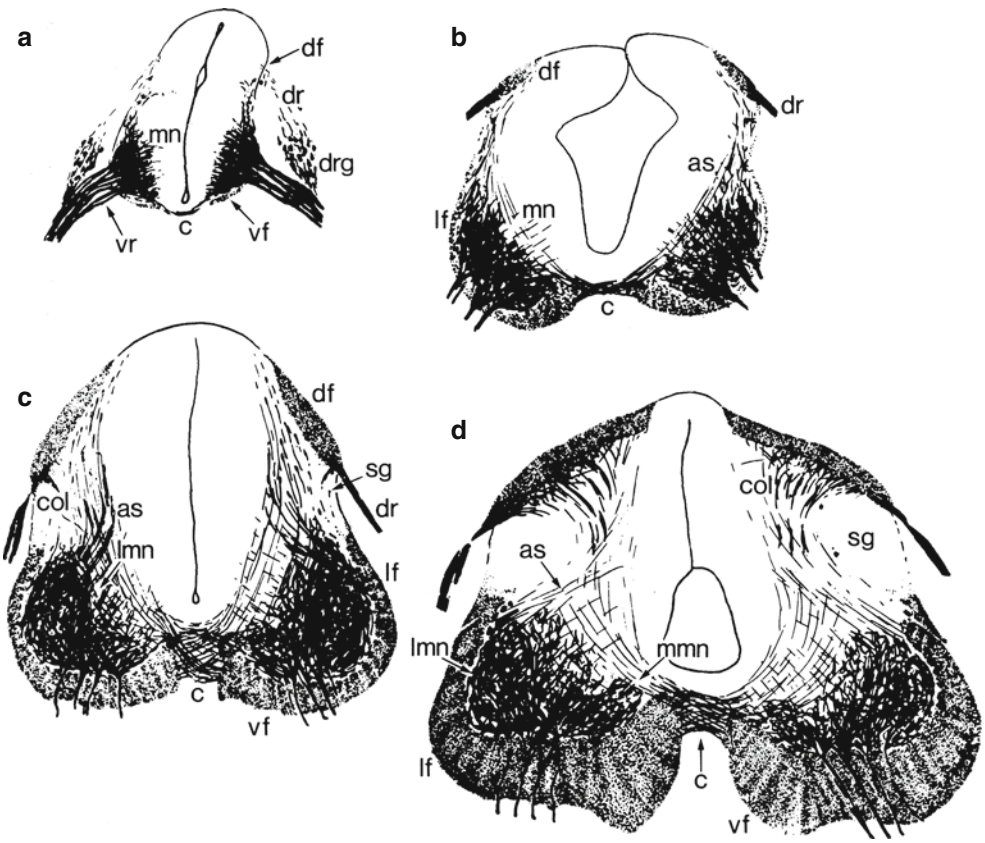

Fig. 6.16 (**a**–**d**) Windle and Fitzgerald's data obtained with silver staining in human embryos of 5–8 weeks of gestation. *as* association interneurons, *c* ventral commissure, *col* dorsal root collaterals, *df* dorsal funiculus, *dr* dorsal root, *drg* dorsal root ganglion, *lf* lateral funiculus, *lmn* lateral motoneurons, *mmn* medial motoneurons, *mn* motoneurons, *sg* substantia gelatinosa, *vf* ventral funiculus, *vr* ventral root (After Windle and Fitzgerald 1937)

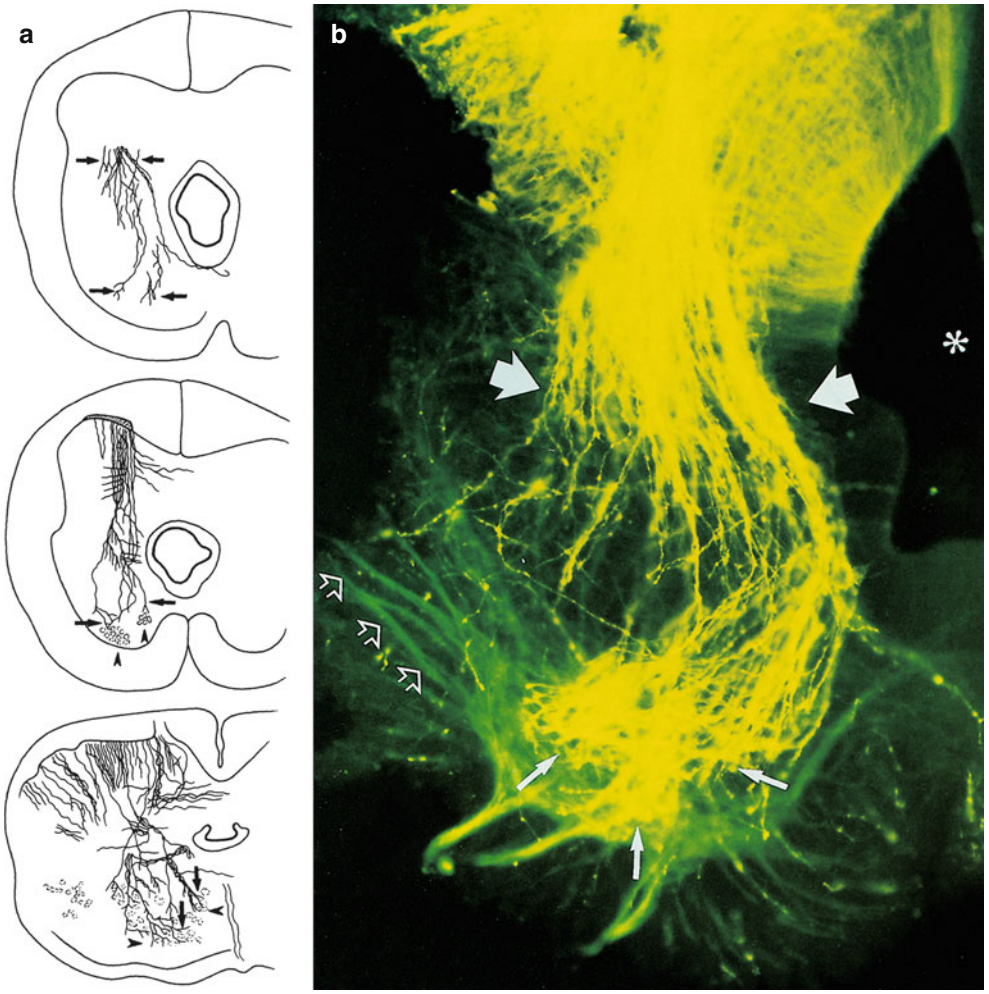

Fig. 6.17 Development of dorsal root projections as found by DiI labelling in the human fetal spinal cord. (**a**) At 8, 11 and 15 weeks gestational age. A few dorsal root fibres reach the motor pool by 8 weeks. These axons traverse the grey matter in fascicles and defasciculate as they approach the motoneurons (*arrowheads*). These afferents elaborate branches (*arrows*) with increasing complexity. (**b**) An example of DiI labelling at 11 weeks of gestation (Reproduced with permission from Konstantinidou et al. 1995; copyright 1995, Wiley-Liss Inc, a subsidiary of John Wiley & Sons, Inc.)

emerge from the lateral aspect of each dorsal funiculus in the brachial region. A few long collateral branches pass into the lateral division of the ventral horn at stage 20. At this stage of development the ventral funiculus contains descending axons from the brain stem passing via the fasciculus longitudinalis medialis (flm). Most of its other fibres are probably ascending, however (Rhines and Windle 1941). Interneurons with ascending projections send their axons to the floor plate where they cross in the ventral commissure and form contralaterally ascending tracts in the ventrolateral funiculus. Therefore, three components of cutaneous reflex pathways (primary afferent fibres, interneurons and motoneurons) are already found in human embryos of 4 postovulatory weeks. A rapid differentiation of these components takes place in embryos of 6 postovulatory weeks (Fig. 6.16d).

Konstantinidou et al. (1995) were able to study the development of the dorsal root projections in the fetal human spinal cord between 8 and 19 weeks of gestation (about 6–17 postovulatory weeks) using 1,1′-dioctadecyl–3,3,3′,3′- tetramethylindocarbocyanine perchlorate (DiI) tracing (Fig. 6.17). Primary afferent fibres were found to enter the spinal grey matter very early in development. By 6 postovulatory weeks, a few dorsal root axons (presumably muscle spindle afferents) already reached the motor pools. As development progresses, these axons project to the ventral horn and branch in a restricted area in the intermediate zone as well as in the motor pools. Between 9 and 17 postovulatory weeks, axon collaterals in the ventral horn form boutons in the proximity of motoneuron somata and their proximal dendrites. Other groups of axons penetrate the spinal grey matter via the mediolateral extent of the dorsal horn to reach lamina IV, and then turn upwards to terminate in layers III and IV. Probably, these axons arise from DRG cells that innervate low-threshold mechanoreceptors.

Okado and co-workers (Okado et al. 1979; Okado 1980, 1981) studied the synaptogenesis in the lateral motor column of the human cervical spinal cord. The first synapses were found in the motor nucleus of the cervical cord in a 10-mm embryo (Carnegie stage 15). Since no dorsal root fibres extend far enough to reach the motor neuropil, these axodendritic synapses probably come from interneurons. The first synapses between dorsal root fibres and interneu-

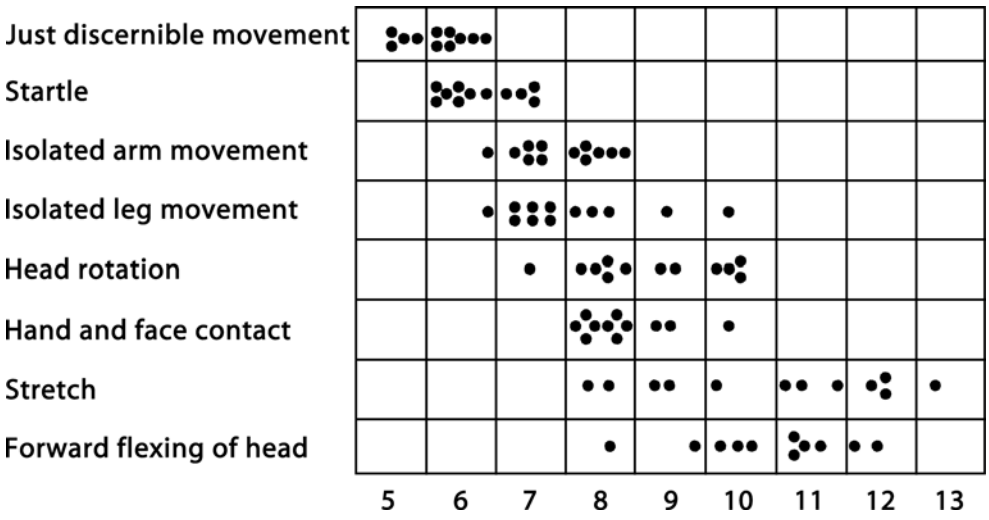

Fig. 6.18 Summary of ultrasonic recordings of the first emergence of certain classes of spontaneous movements in human embryos (After de Vries et al. 1982)

rons as well as the first axosomatic synapses in the motor neuropil were found at stage 17. During the first 5 months of development there appear to be three critical periods of synaptogenesis coinciding with behavioural changes found in human fetuses (Okado and Kojima 1984): (1) a period of closure of the spinal reflex arc, coinciding with the appearance of spinal reflex activities; (2) a period of rapid increase of axodendritic synapses that corresponds with the onset of local activities (Humphrey 1964); and (3) a period with an increase of axosomatic synapses. Peripheral branches of DRG cells reach the palm of the hand by 8.5 weeks of development (Cauna and Mannan 1961) and contact epithelial cells by about 10.5 weeks (Hogg 1941). Innervation of cutaneous receptors starts between 10.5 and 14.5 weeks (Hogg 1941; Cauna and Mannan 1959).

Using real-time ultrasound, de Vries et al. (1982, 1984) found the first discernible spontaneous movements of the fetus at 7.5 weeks of gestation (about 5.5 postovulatory weeks or approximately stage 16), as already suggested by Hooker's (1938, 1954) experiments on aborted embryos. By the end of the embryonic period, the following types of prenatal movements are discernable by ultrasound (Fig. 6.18): startles, general movements, hiccups, isolated limb movements, head retroflexion and rotation, and hand-face contact. Such movements reflect coordinated motor patterns (de Vries et al. 1982, 1984; Natsuyama 1991). By this time, descending supraspinal pathways arising in the interstitial nucleus of the flm, the reticular formation of the brain stem and the vestibular nuclear complex must have reached the spinal cord (Sect. 6.7). Arm and leg movements develop at 9–12 weeks and by about 16 weeks' postmenstrual age all fetuses show the entire fetal repertoire. This repertoire continues to be present throughout gestation (Hadders-Algra and Forssberg 2002; Kurjak et al. 2009; Salihagic-Kadic et al. 2009).

6.6 Development of Spinal Ascending Projections

The ascending sensory pathways from the spinal cord can be divided into three groups (Willis and Coggeshall 1991): (1) pathways for tactile information, vibration and position sense, carried via several pathways, the dorsal funiculus or column in particular; (2) pathways for pain and temperature, i.e. the spinothalamic tract which is accompanied by fibres terminating in the reticular formation (spinoreticular fibres) and fibres to the mesencephalon (spinomesencephalic fibres); and (3) pathways for somatosensory information to the cerebellum (Chap. 8). In the large-fibred **dorsal column-medial lemniscus system**, there is a bundling together of elements with common modality and receptor field properties (Mountcastle 1984; ten Donkelaar et al. 2011). This bundling begins in the **first-order** or **primary afferent fibres**, which in turn project upon similarly modularized elements of the dorsal column nuclei (Fig. 6.19). The **second-order afferent fibres** arising in the dorsal column nuclei (the gracile and cuneate nuclei) cross the midline as the *internal arcuate fibres* in the caudal medulla and ascend in the prominent **medial lemniscus** to modules of the ventrobasal complex in the thalamus (Chap. 9). Here, **third-order afferent fibres** pass to cell columns of the postcentral gyrus.

The **anterolateral funiculus** or **ventral quadrant** of the human spinal cord contains pathways that are crucial for pain and temperature sensations (Fig. 6.20). The **spinothalamic tract** has long been regarded as the major pathway responsible for evoking pain sensations. Other pathways involved in pain transmission are the spinomesencephalic, spinohypothalamic and spinolimbic tracts (Willis and Westlund 2004; ten Donkelaar et al. 2011). Nociceptive information from the skin is distributed in the spinal cord to layers I, II and V, whereas visceral input terminates largely in

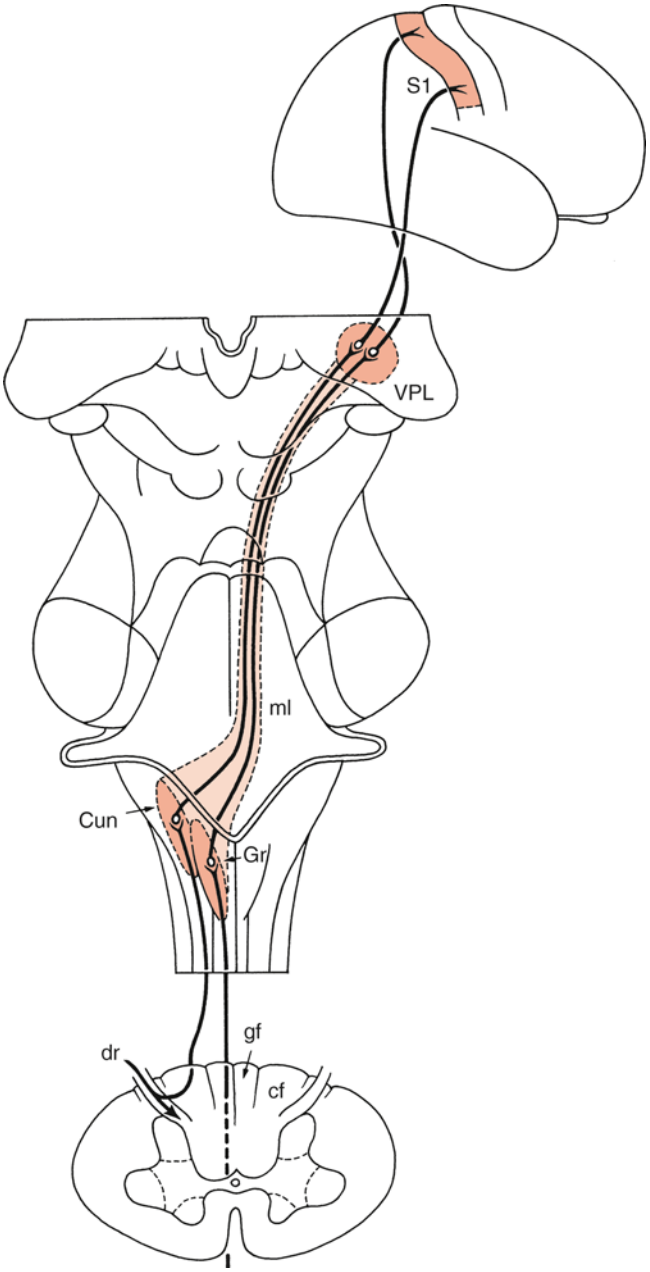

Fig. 6.19 Overview of the human ascending spinal system for gnostic sensibility. *cf* cuneate fascicle, *Cun* cuneate nucleus, *dr* dorsal root, *gf* gracile fascicle, *Gr* gracile nucleus, *ml* medial lemniscus, *S1* primary somatosensory cortex, *VPL* ventroposterior lateral nucleus (After ten Donkelaar et al. 2007)

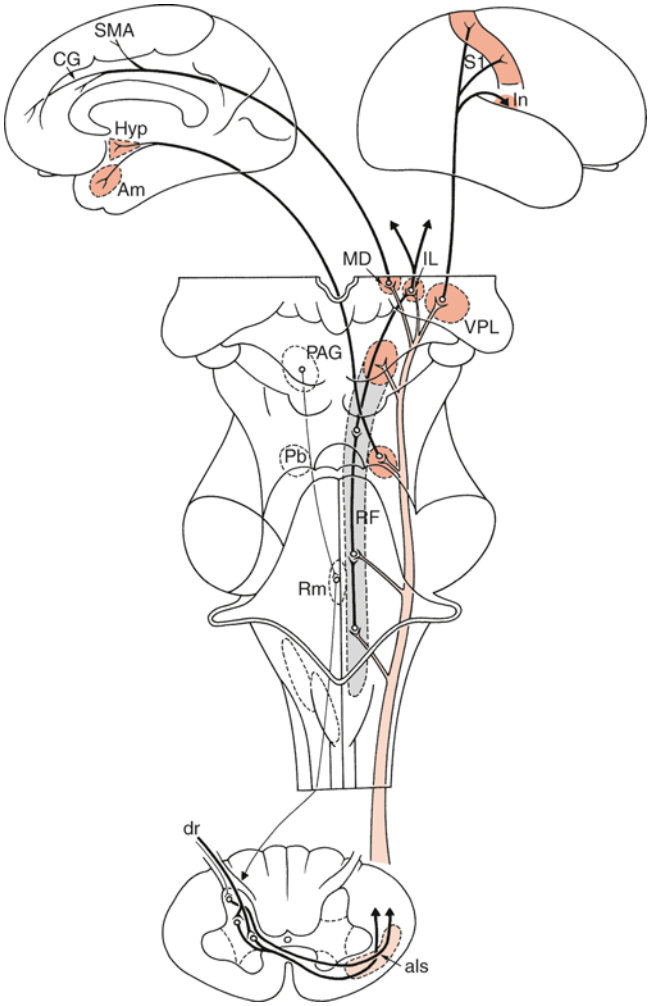

Fig. 6.20 Overview of the human ascending spinal systems for vital sensibility. *als* anterolateral system, *Am* amygdala, *CG* cingulate gyrus, *dr* dorsal root, *Hyp* hypothalamus, *IL* intralaminar nuclei, *In* insula, *MD* mediodorsal nucleus, *PAG* periaqueductal grey, *Pb* parabrachial nucleus, *RF* reticular formation, *Rm* raphe magnus nucleus, *SMA* supplementary motor area, *S1* primary somatosensory cortex, *VPL* ventroposterior lateral nucleus (After ten Donkelaar et al. 2007)

layers I and V. Neurons that relay nociceptive information to the brain stem are located largely in layers I, III, V-VII and X. The pathway arising from layer I has received considerable attention such that many of the functions once associated with the pathway arising from the deeper spinal layers are now being reallocated to the pathway arising from the most superficial layers of the dorsal horn (Craig 2003; Willis and Westlund 2004).

Ascending spinal tract neurons begin to differentiate as early as E12 (Altman and Bayer 1984). Waldeyer's cells in the marginal zone, a major source of contralaterally projecting spinothalamic fibres, and several other cells in the intermediate zone giving rise to spinocervical, rostral and ventral spinocerebellar, and some spinothalamic fibres are produced at E12 and E13. The neurons of Clarke's column giving rise to the dorsal spinocerebellar tract are formed at E13. Most neurons of the intermediate zone are generated at E13 and E14. Beal and Bice (1994) showed that lumbar spinothalamic and spinocerebellar neurons are generated between E13 and E15. The primary afferent projections from dorsal root fibres to the dorsal column nuclei also arise prenatally (Chimelli and Scaravilli 1987; Wessels et al. 1991). Projections from the dorsal column nuclei

reach the thalamus by the day of birth (Asanuma et al. 1988). Lakke (1997) found the first spinothalamic fibres, anterogradely labelled from cervical injections, in the anterior thalamus at E18.

In human embryos, the dorsal funiculus has reached the caudal brain stem at stage 16, i.e. at about 37 postovulatory days (Müller and O'Rahilly 1989a). Cuneate and gracile decussating fibres forming the medial lemniscus are present at stage 20 (Müller and O'Rahilly 1990a, b). Altman and Bayer (2001; Bayer and Altman 2002) studied the growth and maturation of spinal fibre tracts, using the following criteria for maturation: (1) their absence or presence; (2) onset of proliferative gliosis; (3) onset of reactive gliosis; (4) advanced reactive gliosis; (5) onset of myelination; and (6) advanced myelination (Table 6.3). The cuneate and gracile fasciculi become myelinated by the middle of the third trimester, the cuneate before the gracile fascicle. Using, myelin basic protein (MBP) immunohistochemistry, Weidenheim and co-workers (Weidenheim et al. 1992, 1993, 1996; Bodhireddy et al. 1994) showed that in the gracile fascicle myelination starts at the lumbar level. The dorsal spinocerebellar tract is absent or poorly developed at the beginning of the second trimester (Altman and Bayer 2001). It is present above the lateral corticospinal tract in 20-week-old fetuses. Onset of reactive gliosis in this fibre tract starts in the 26th week of development, and its myelination is evident from 33 weeks onwards. The maturation of the ventral spinocerebellar tract may lag behind that of the dorsal spinocerebellar tract. The spinothalamic tract develops relatively late. It is either absent or very slender in 14-week-old fetuses, and can be delineated from intraspinal tracts by the presence of fewer reactive glia. Reactive gliosis is advanced at 33 weeks and in the perinatal period. Myelination of the spinothalamic tract begins in the late-term neonate.

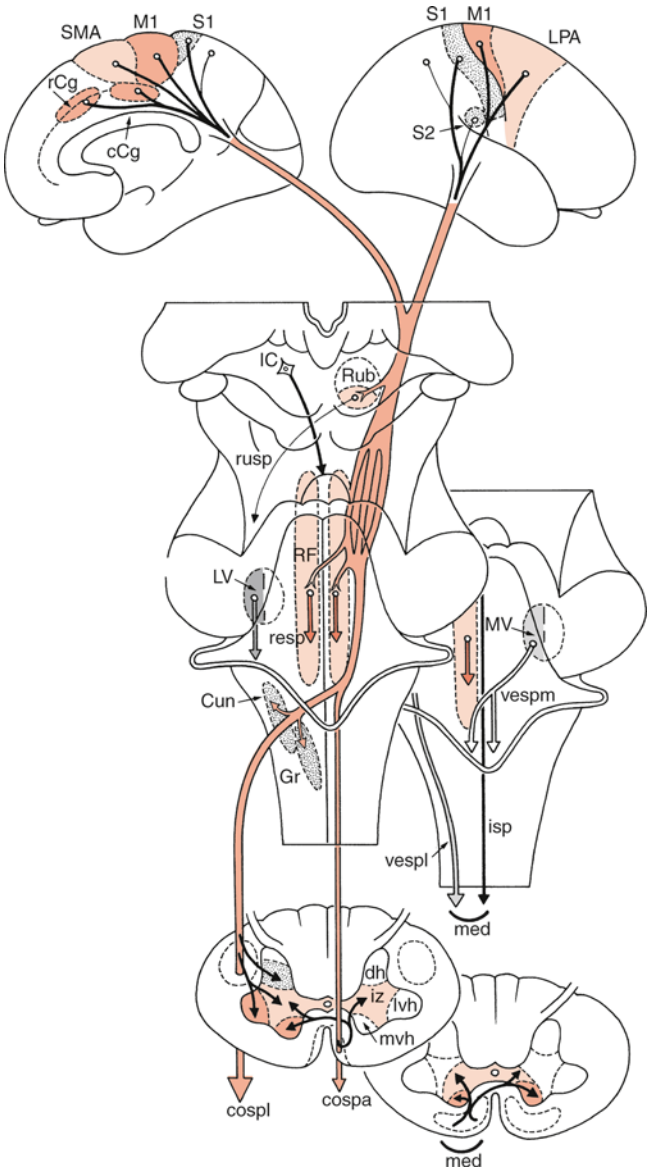

Fig. 6.21 Overview of human descending supraspinal systems *cCg* caudal cingulate motor area, *cospa*, *cospl* anterior and lateral corticospinal tract, *Cun* cuneate nucleus, *dh* dorsal horn, *rCg* rostral cingulate motor area, *Gr* gracile nucleus, *IC* interstitial nucleus of Cajal, *isp* interstitiospinal tract, *iz* intermediate zone, *LPA* lateral premotor area, *lvh*, *mvh* lateral and medial parts of ventral horn, *LV*, *MV* lateral and medial vestibular nuclei, *med* medial system, *M1* primary motor cortex, *resp* reticulospinal tract, *RF* reticular formation, *Rub* red nucleus, rusp rubrospinal tract, *SMA* supplementary motor area, *S1*, *S2* primary and secondary somatosensory cortices, *vespl*, *vespm* lateral and medial vestibulospinal tracts (After ten Donkelaar et al. 2007)

6.7 Development of Descending Projections to the Spinal Cord

Descending pathways for the control of spinal motor neurons arise in the cerebral cortex, in the hypothalamus and in various brainstem structures, including the reticular formation and the vestibular nuclear complex (Kuypers 1981; Nathan and Smith 1981; Holstege 1991; Nathan et al. 1990, 1996; ten Donkelaar 2000, 2011; Fig. 6.21). As regards the course and site of termination of the descending pathways to the spinal cord, a classification can be made into lateral and medial systems (Kuypers 1981). Interstitiospinal, reticulospinal and vestibulospinal pathways from the brain stem pass via the ventral funiculus and ventral parts of the lateral funiculus, and terminate in the mediodorsal parts of the ventral horn and adjacent parts of the intermediate zone. This medial system is functionally related to postural activities and progression, and constitutes a basic system by which the brain exerts control over movements. The lateral system is composed of rubrospinal, some reticulospinal and raphespinal fibres, arising in a rostral, magnocellular part of the medullary raphe nucleus, and the corticospinal tract, all passing via the dorsal part of the lateral funiculus. In vertebrates, the

rubrospinal tract terminates in the dorsolateral part of the intermediate zone and plays an important role in the steering of limb movements (ten Donkelaar 2000). The human rubrospinal tract is indistinct (Nathan and Smith 1981) and is superseded by the corticospinal tract. The corticospinal tract arises from layer V pyramidal cells, particularly from rostral, frontal parts of the cerebral cortex (Chap. 10).

The formation of the descending supraspinal pathways occurs according to a developmental sequence. In all tetrapods studied (ten Donkelaar 2000), reticulospinal and interstitiospinal fibres reach the spinal cord first, followed by vestibulospinal fibres and, much later, by rubrospinal and, if present, corticospinal projections. Throughout vertebrates including humans, the flm is the first descending pathway to be formed. Interstitiospinal fibres 'pioneer' this tract, and are joined by reticulospinal fibres. Vestibulospinal fibres (the medial vestibulospinal tract) follow much later. The early-arising lateral vestibulospinal tract and the late-arriving rubrospinal and corticospinal tracts take a separate course through the brain stem.

6.7.1 Descending Projections from the Brain Stem

In rats, early brainstem-spinal cord projections were studied using the carbocyanine dye DiI in fixed embryos (Auclair et al. 1993, 1999; de Boer-van Huizen and ten Donkelaar 1999), and biotinylated dextran amine (BDA) in an isolated embryonic brain-spinal cord preparation (de Boer-van Huizen and ten Donkelaar 1999). With both techniques it was shown that in embryos at least 12 days of age (E12), i.e. at the time of closure of the posterior neuropore (Theiler stage 12), a variety of brain stem centres already innervates the spinal cord (Table 6.2). In the interstitial nucleus of the flm and various parts of the reticular formation – mesencephalic, pontine as well as medullary – mainly large immature, bipolar labelled neurons were observed. In later stages (E13, E14), the number of labelled neurons increased and more mature, multipolar cells were found. At E13 (stage 15), labelled neurons were also observed in the vestibular nuclear complex. Raphespinal neurons were not labelled before E14 (stage 17). Just below the cerebellum a conspicuous small group of neurons was found labelled in a position reminiscent of the locus coeruleus. In their extensive birthdating studies in rats, Altman and Bayer (1980a, b, c, d, 1981) showed that (1) neurons in the medullary reticular formation are produced between E11 and E15 along a caudorostral gradient; (2) those in the pontine reticular formation are generated even earlier; (3) large vestibular neurons in the lateral (Deiters) nucleus are generated before the smaller neurons in other vestibular nuclei; (4) neurons in the locus coeruleus are produced mostly at E12; and (5) neurons in the nucleus of Darkschewitsch, related to the interstitial nucleus of the flm for which no data are available, are produced at E12 and E13 (Table 6.2). Comparison of the data on the time of origin with those on the ingrowth of brain stem fibres into the cord suggests that interstitiospinal and reticulospinal neurons start projecting spinalwards shortly after they are generated. Since the distance to the site of tracer application for the interstitial nucleus of the flm and the pontine reticular formation by far exceeds that of the medullary reticular formation, it is most likely that interstitiospinal and pontine reticulospinal axons are the first supraspinal fibres to invade the spinal cord. Kudo et al. (1993) and Lakke (1997) studied the gradual descent of supraspinal fibres into the spinal cord. At E17, fibres from the lateral vestibular nucleus, the serotonergic raphe magnus nucleus and the gigantocellular reticular nucleus have reached lumbosacral levels, followed at E18 by fibres from many other brain stem nuclei. Last to arrive prenatally (E21) are the rubrospinal and medial vestibulospinal tracts. Hypothalamospinal fibers reach the lumbosacral cord on P1.

Assuming that the stages of neural development are similar in rats and humans even though their exact chronological ages are different, Bayer et al. (1995) estimated human neurogenetic timetables by extrapolating the rat data to the longer span of human development. Most brain stem nuclei innervating the spinal cord are born between 4 and 7 weeks after fertilization (Table 6.2). The first descending brain stem projections to the spinal cord in human embryos arise in the interstitial nucleus of the flm and in the reticular formation. Descending fibres from the medullary reticular formation reach the spinal cord in embryos of 10–12-mm crown-rump length (CRL; Windle and Fitzgerald 1937). Interstitiospinal fibres from the interstitial nucleus of the flm start to descend in the flm at stage 13 (Fig. 6.22), i.e. at E28 (Müller and O'Rahilly 1988a, b). In 12-mm-CRL embryos (about stage 17/18), vestibulospinal projections were found (Windle 1970). The red nucleus can first be recognized in stage 17 embryos (Cooper 1946; Müller and O'Rahilly 1989b), but data on the development of a rubrospinal tract are not available. At the end of the embryonic period, the flm is well-developed, and receives ascending and descending (the medial vestibulospinal tract) components from the vestibular nuclear complex (Müller and O'Rahilly 1990b). The lateral vestibular tract arises from the lateral (Deiters) vestibular nucleus.

Monoaminergic projections also appear to arise early in human development. In 8-mm-CRL embryos (about stage 14), Windle and Fitzgerald (1942) observed that descending fibres from the presumptive locus coeruleus join the lateral longitudinal fascicle. A definite locus coeruleus can be distinguished at stage 17 (Müller and O'Rahilly 1989b). Olson et al. (1973) detected neurons containing catecholamines or serotonin in embryonic brains as early as 8 weeks (21-mm CRL), and some catecholaminergic medullary neurons with spinal projections in 10-week-old fetuses

Table 6.2 The development of descending supraspinal projections in rats and humans

Nuclei	Time of neuron origin in rats[a]	Innervation of high cervical cord in rats[b]	Innervation of lumbosacral cord in rats[c]	Estimated time of neuron origin in humans (postovulatory weeks)[d]	Estimated innervation of the cervical spinal cord in humans (Carnegie stages)
Reticular formation					
Medullary	E11-E15	E12	E17/19	4.1–7.0	~14/15[e]
Pontine	<E11-E15	E12	E18	4.1–7.0	
Mesencephalic	Unknown	E12	E18	5.3–7.0	
Interstitial nucleus flm	Unknown	E12	E18	4.1–5.7 (related Darkschewitsch nucleus)	14?[f, g]
Raphe nuclei	E11-E15	E14	E17	3.5–7.0	
Serotonergic projections[h]		E14	E17		?
Vestibular nuclei					
Lateral vestibular nucleus	E11-E14	E13	E17	4.1–5.7	~17/18[g]
Medial and inferior vestibular nuclei	E12-E15	?	E18-E21	4.1–7.0	Before end of embryonic period[f, g]
Locus coeruleus					
Coeruleospinal neurons	Peak E12	E12?	E20	Peak 4.1–5.2	
Noradrenergic projections[i]		<E16	E17/18		18[j]
Red nucleus	E13-E14	E17[k]	E21[k]	5.3–6.6	?
Hypothalamus					
Paraventricular nucleus	Peak E14-E15		P1	5.3–7.0	?
Corticospinal projections	Peak E15-E17	P0[l]	P7-P9[l]	(5.8) 6.7–9.9	Early fetal period[m]

After ten Donkelaar (2000)

References: [a]Altman and Bayer (1980a, b, c, d, 1981); [b]de Boer-van Huizen and ten Donkelaar (1999), [c]Lakke (1997), [d]Bayer et al. (1995); [e]Windle and Fitzgerald (1937), [f]Müller and O'Rahilly (1988a, b, 1990b); [g]Windle (1970), [h]Rajaofetra et al. (1989), [i]Rajaofetra et al. (1992), [j]Puelles and Verney (1998), [k]Lakke and Marani (1991), [l]Gribnau et al. (1986), [m]Humphrey (1960)

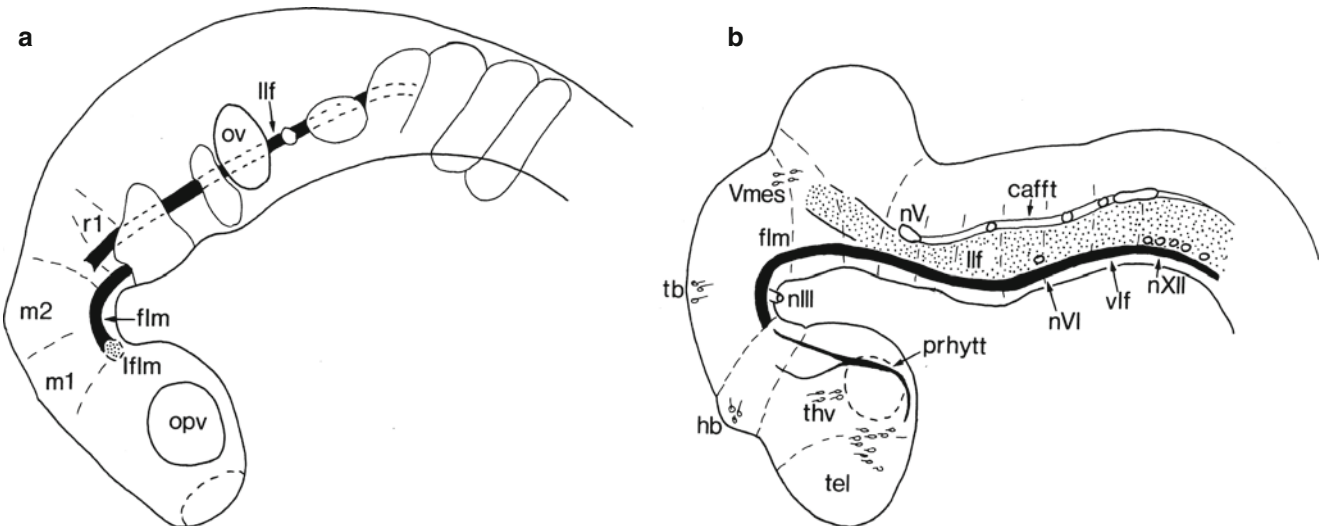

Fig. 6.22 The extent of the fasciculus longitudinalis medialis (*flm*) and other longitudinal tracts in stage 13 (**a**) and 14 (**b**) human embryos. *cafft* central afferent tract, *hb* habenula, *Iflm* interstitial nucleus of the flm, *llf* lateral longitudinal tract, *m1*, *m2* mesomeres, *nIII*, *nV*, *nVI*, *nXII* cranial nerves, *opv* optic vesicle, *ov* otic vesicle, *prhytt* pretectohypothalamic tract, *r1* rhombomere 1, *tb* tectobulbar tract, *tel* telencephalon, *thv* ventral thalamus, *vlf* ventrolateral fascicle, *Vmes* mesencephalic nucleus of the trigeminal nerve (After Müller and O'Rahilly 1988a, b)

(40–45-mm CRL). Using antibodies against enzymes of the catecholaminergic pathway, noradrenergic cell groups were labelled in the medulla obongata and in the locus coeruleus as early as 6 weeks of gestation (Verney et al. 1991; Zecevic and Verney 1995; Puelles and Verney 1998).

Fibre tracts that appear early in development generally undergo myelination before later-appearing tracts (Yakovlev and Lecours 1967; Gilles et al. 1983; Brody et al. 1987; Kinney et al. 1988; Altman and Bayer 2001; Table 6.3). In the brain stem, myelination starts in the flm

Table 6.3 Development of myelination of the main fibre tracts in the human spinal cord

Fibre tract	First evidence of myelin basic protein staining	Onset of reactive gliosis	Onset of myelination
Ascending tracts			
Cuneate fascicle	14 gestational weeks	20 gestational weeks	At 33 gestational weeks, myelination well advanced throughout
Gracile fascicle	16 gestational weeks	20 gestational weeks	At 33 gestational weeks, wedge area myelinating
Dorsal spinocerebellar tract	20 gestational weeks	26 gestational weeks	33 gestational weeks
Ventral spinocerebellar tract	20 gestational weeks	Later than dorsal spinocerebellar tract	Late third trimester
Spinothalamic tract	20 gestational weeks	33 gestational weeks	Late-term neonate
Descending tracts			
Vestibulospinal tracts	9.5 gestational weeks	By 20 gestational weeks, first sign of reactive gliosis in medial vestibulospinal tract	33 gestational weeks
Reticulospinal tracts	9.5 gestational weeks	Comparable to vestibulospinal tracts	33 gestational weeks
Corticospinal tracts			
Lateral corticospinal tract		At birth few glia present	After birth
Anterior corticospinal tract		At birth few glia present	After birth

After Weidenheim et al. (1993, 1996), Altman and Bayer (2001)

at 8 postovulatory weeks. The vestibulospinal tracts become myelinated at the end of the second trimester, whereas the pyramidal tracts begin very late (at the end of the third trimester). Early myelination of spinal pathways was studied using antibodies against myelin-associated proteins, MBP in particular (Tohyama et al. 1991; Weidenheim et al. 1992, 1993, 1996; Bodhireddy et al. 1994). The temporal and spatial MBP expression in the first and early second trimester of the human spinal cord is shown in Fig. 6.23. MBP is expressed in a rostral-to-caudal and anterolateral-to-posterior manner in most tracts of the spinal cord. In the fasciculus gracilis, however, myelination starts at the lumbar level.

6.7.2 Development of the Pyramidal Tract in Rodents

Data on the early outgrowth and guidance of corticospinal tract axons in rodents are discussed in Chap. 2. In rats and mice, corticospinal fibres do not reach upper cervical spinal segments before birth (Schreyer and Jones 1982; Terashima et al. 1983; Gribnau et al. 1986). The vast literature on the **outgrowth** of the rodent **corticospinal tract** has been summarized in several reviews (Stanfield 1992; O'Leary and Koester 1993; Terashima 1995a; Joosten and Bär 1999). In rats, the postnatal development of the corticospinal tract can be divided into three periods: (1) an outgrowth phase (P1-P10); (2) a myelination phase (P10-P28); and (3) a maturation phase (P28-adult). A delay of 2 days was found between the arrival of corticospinal axons at a certain level of the spinal cord and their ingrowth into the spinal grey matter. Initially, most parts of the cerebral cortex including the occipital lobe innervate the spinal cord (Stanfield and O'Leary 1985; O'Leary and Stanfield 1986; Joosten et al. 1987). Axons from frontal regions arrive first and those from the occipital lobe come last. The withdrawal of collaterals accounts for the dramatic loss of fibres from the corticospinal tract during development (Schreyer and Jones 1988). In early development corticospinal projections also have transient *ipsilateral* projections that are predominantly eliminated when maturity is reached (Joosten et al. 1992; O'Leary et al. 1992; Oudega et al. 1994).

In the development of cortical axons arising from layer V neurons three stages can be distinguished (O'Leary et al. 1990; Chap. 2): (1) layer V axons extend out of the cortex towards the spinal cord, bypassing their subcortical targets; (2) the subcortical targets are exclusively contacted by axon collaterals that develop by delayed interstitial branching off the flank of a spinally directed primary axon; and (3) specific branches and segments of the primary axon are selectively eliminated to yield the mature projections functionally appropriate for the area of cortex in question. In mutant rodents with extensive perturbations in the development of the cerebral cortex such as the reeler mouse and the shaking rat Kawasaki, corticospinal tract neurons are spread throughout all layers of the mutant cortex (Terashima et al. 1983; Inoue et al. 1991; Ikeda and Terashima 1997; Chap. 10). The specificity of corticospinal connections is relatively unaffected (Terashima 1995a, b). Myelination of the rat pyramidal tract starts in the caudal medulla at P7 (Gorgels 1990, 1991). Myelination of corticospinal axons in the spinal

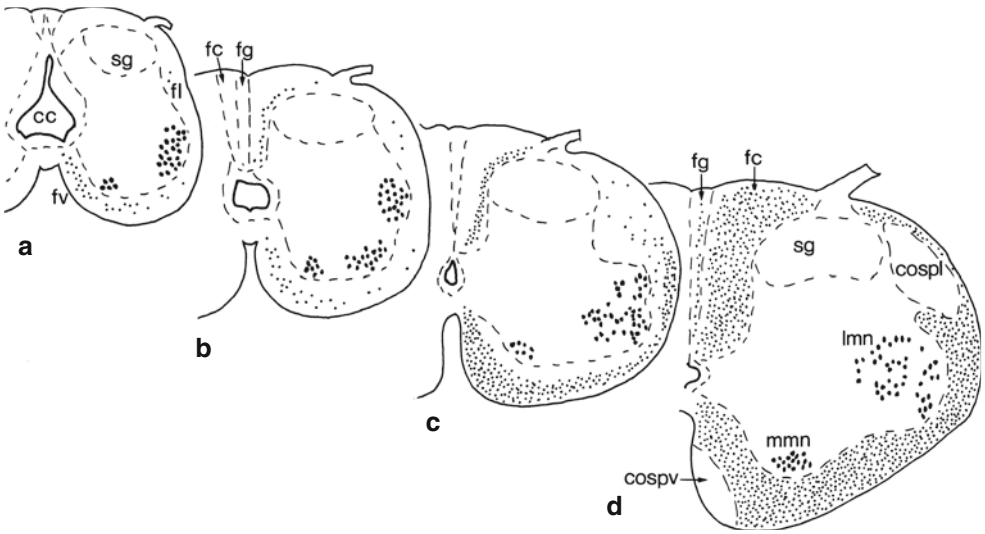

Fig. 6.23 The development of myelination in the early human spinal cord as found by the expression of myelinated basic protein. (**a**–**d**) Transverse sections through the cervical spinal cord of specimens 10, 12, 16 and 23 gestational weeks of age, respectively. *cc* central canal, *cospl* lateral corticospinal tract, *cospv* ventral corticospinal tract, *fc* fasciculus cuneatus, *fg* fasciculus gracilis, *fl* lateral funiculus, *fv* ventral funiculus, *lmn* lateral motoneuron column, *mmn* medial motoneuron column, *sg* substantia gelatinosa (Based on data by Weidenheim et al. 1993, 1996; Bodhireddy et al. 1994)

cord begins rostrally (C5) at about P14 and continues caudalwards during the third postnatal week (Joosten et al. 1989). A close temporal relationship exists between the appearance of the forelimb and hindlimb placing responses and the arrival of corticospinal axons in the spinal grey matter (Donatelle 1977). Forelimb placing is first seen between P4 and P7, and hindlimb placing between P9 and P13.

Several **mechanisms** control **corticospinal fibre outgrowth** into their target areas (O'Leary et al. 1990; Joosten and Bär 1999). A diffusible chemotropic signal is one of the environmental cues involved in axonal outgrowth and guidance. The pons becomes innervated by controlling the budding and directed outgrowth of corticospinal axon collaterals through the release of a diffusible chemotropic substance (Heffner et al. 1990; O'Leary et al. 1990). The same holds for the cervical spinal grey matter (Joosten et al. 1991). The neuron-specific phosphoprotein B-50 (or GAP43), a major substrate of kinase C in fetal nerve growth cones, is strongly expressed during the outgrowth of the pyramidal tract (Gorgels et al. 1987). The cell adhesion molecule L1 (L1CAM) may be involved in fascicle formation of outgrowing, later-arriving corticospinal fibres (Joosten et al. 1990; Fujimori et al. 2000). In L1 mutant mice, the L1 mutation causes a primary pathfinding deficit in the development of the corticospinal decussation (Cohen et al. 1997; Dahme et al. 1997; Castellani et al. 2000). A varying, but reduced number of corticospinal fibres was observed in the posterior columns of L1-deficient mice. These fibres did not extend beyond cervical levels. Moreover, a substantial number of corticospinal axons failed to cross the midline.

As they navigate through the internal capsule, corticofugal axons, which express *Robo1* and *Robo2*, are restricted to the corticospinal tract by Slit1 and Slit2, which are expressed in the ganglionic eminences as well as in the basal telencephalon and in the midline (Bagri et al. 2002; Izzi and Charron 2011; Fig. 6.24). *Slit1*/*Slit2* and *Robo1*/*Robo2* mutant mice display corticofugal axon fascicles that are ventrally displaced in the basal telencephalon and a few of these axons also aberrantly cross the midline targeting the contralateral corticospinal tract (Bagri et al. 2002: López-Bendito et al. 2007; Izzi and Charron 2011). Dcc and Unc5hc, which are expressed by corticospinal axons are thought to interact with Netrin-1 expressed at the midline to replace pyramidal decussation (Finger et al. 2002).

Various **mechanisms** are involved in the proper **decussation** of the pyramidal tract. During its outgrowth, Joosten and Gribnau (1989) noted a prominent vimentin-immunoreactive glial septum in the midline raphe of the hindbrain and spinal cord. Such a glial septum is absent in the decussation area of corticospinal tract fibres. This glial septum may act as a physical barrier during the outgrowth of the corticospinal tract by preventing its decussation. Oligodendrocytes and CNS myelin contain potent, membrane-bound inhibitors of neurite growth (Caroni and Schwab 1988a, b). Oligodendrocyte-associated neurite growth inhibitors (NI-35 and NI-250) in the earlier myelinated cuneate and gracile fascicles play an important role in channelling and 'guard-rail' function to keep the corticospinal tract axons in a compact tract and to prevent the ingrowth into the neighbouring sensory tracts (Schwab and

Schnell 1991). Through Eph receptors, ephrin-B3 may function as a midline-anchored repellent that prevents corticospinal fibres from crossing back into the ipsilateral side of the spinal cord (Kullander et al. 2001; Yokoyama et al. 2001). Ephrin-B3, a ligand for the receptors EphB3 and EphA4, has a restricted expression pattern along the midline of the neural tube (Bergemann et al. 1998; Imondi et al. 2000). EphA4 is expressed in postnatal corticospinal neurons as their axons find their way down the contralateral spinal cord (Dottori et al. 1998). In *ephrin-B3* mutant and in EphA4-deficient mice, corticospinal tract axons fail to respect the midlline boundary of the spinal cord and innervate both contralateral and ipsilateral motoneuron populations (Coonan et al. 2001; Yokoyama et al. 2001). Netrin-1 receptors are also necessary for a proper decussation of the pyramidal tract (Finger et al. 2002). *Robo3* promotes crossing of pyramidal tract axons. In *Robo3*-deficient mice, axons fail to cross the midline (Sabatier et al. 2004; Izzi and Charron 2011).

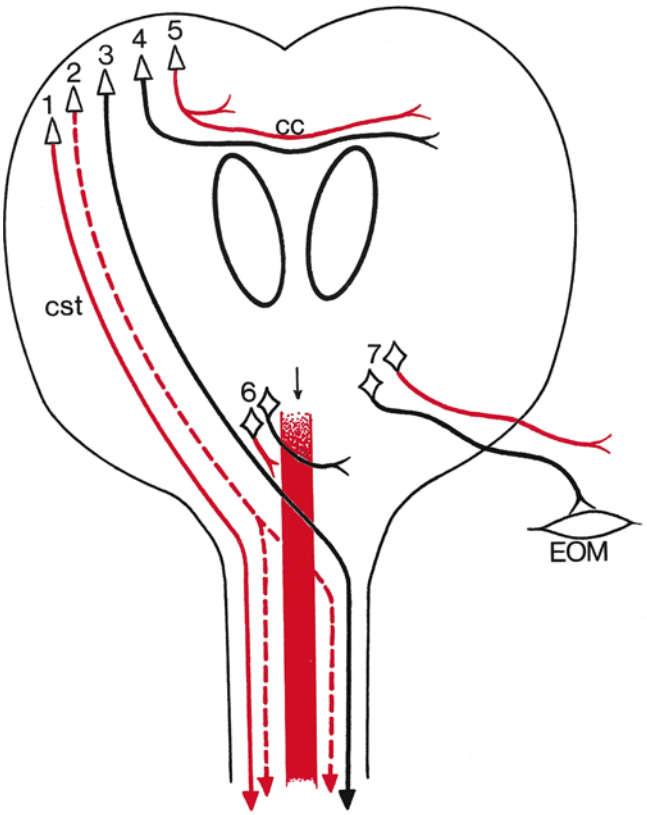

Fig. 6.24 Summary of axon guidance defects in the corticospinal tract (*cst*). With normal guidance (*3*), corticospinal axons navigate from the motor cortex to the spinal cord, decussationg in the medulla. Corpus callosum axons (*4*) and certain hindbrain interneurons (*6*) normally decussate. In HGPPS, corticospinal axons (*1*) and hindbrain interneurons (*6*) fail to decussate resulting in ipsilateral projections. In CMM, some corticospinal axons decussate properly (*2*), whereas others fail to do so and project ipsilaterally. In CFEOM3, there is a variable thinning of the corpus callosum (*5*) and abnormal guidance of the oculomotor nerve (*7*), resulting in dysinnervation of extraocular eye muscles (*EOM*) (After Izzi and Charron 2011)

6.7.3 Development of the Pyramidal Tract in Macaque Monkeys

In the rhesus monkey, corticospinal fibres have reached at least to the level of the lower cervical segments at birth (Kuypers 1962; Fig. 6.25). Tract-tracing experiments in fetal macaque monkeys show that the areal distribution of corticospinal neurons in the cerebral cortex is greater than in mature macaques (Galea and Darian-Smith 1995; Killackey et al. 1997). Both the areal distribution of the cortical origin and the relative number of corticospinal neurons with spinal axons regress very substantially over a period of 2 years (Galea and Darian-Smith 1995). Only a small ipsilateral component remains (Galea and Darian-Smith 1995). Direct corticomotoneuronal projections do not develop until 6–8 months of age. Lawrence and Hopkins (1976) extensively studied the development of hand and finger movements in infant rhesus monkeys. The earliest signs of reaching were found at 3–4 weeks of age. Reaching was inaccurate and grasping of food was part of a rather gross

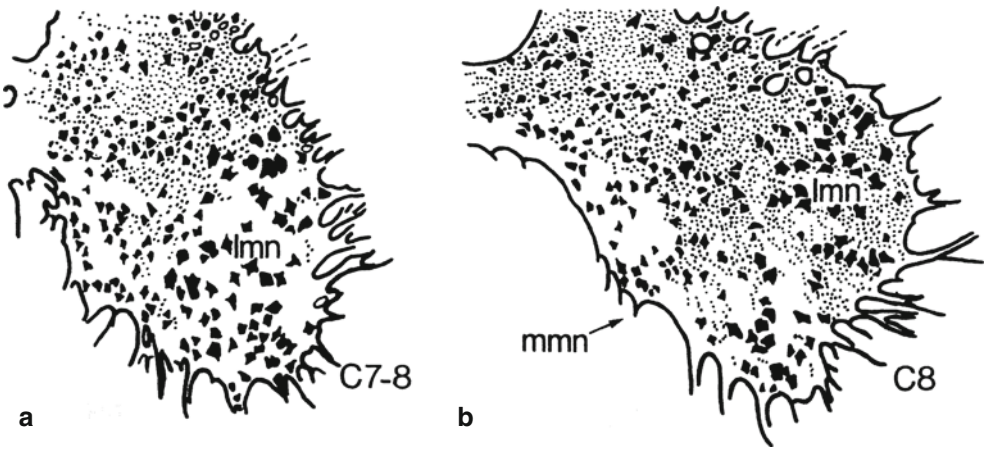

Fig. 6.25 The distribution of corticospinal terminations in the ventral horn of the rhesus monkey: (**a**) at 4 days of development; (**b**) in an adult. *lmn* lateral motoneurons, *mmn* medial motoneurons (After Kuypers 1962)

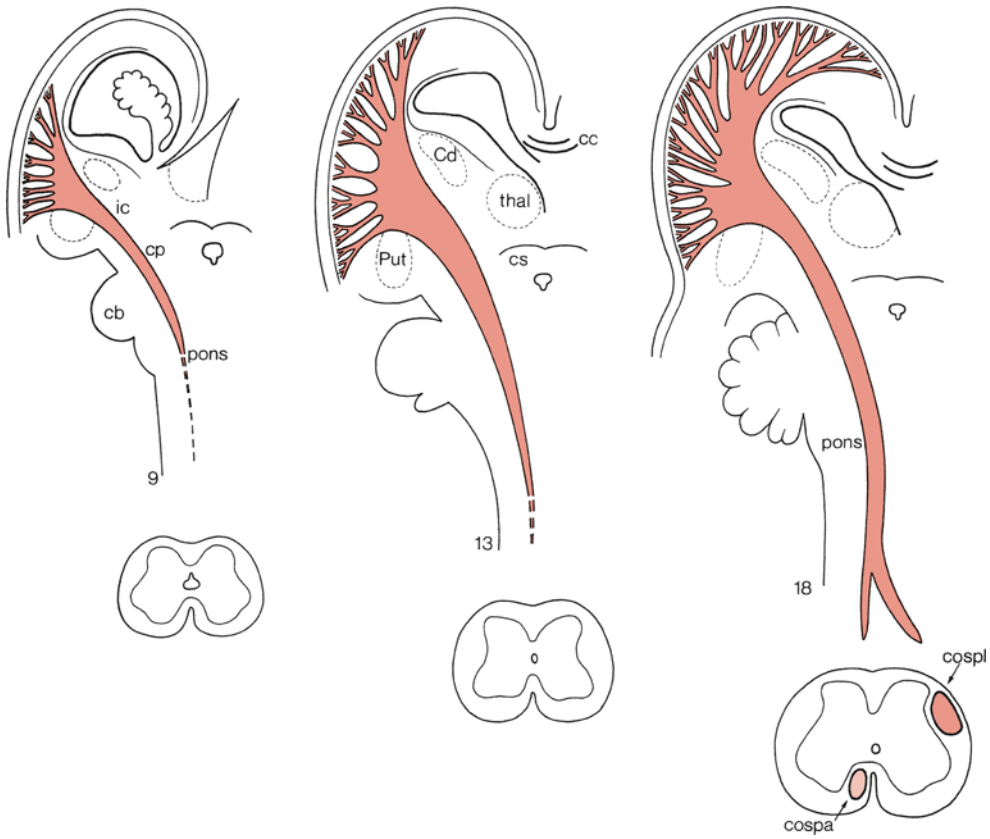

Fig. 6.26 The outgrowth of the human corticospinal tract through the brain stem, shown for 9, 13 and 18 gestational weeks. *cb* cerebellum, *cc* corpus callosum, *Cd* caudate nucleus, *cospa* anterior corticospinal tract, *cospl* lateral corticospinal tract, *cp* cerebral peduncle, *cs* colliculus superior, *ic* internal capsule, *Put* putamen, *thal* thalamus (After Humphrey 1960; Altman and Bayer 2001)

whole arm and hand movement. Smooth reaching occurred in the third month and relatively independent finger movements developed between the second and eighth month. This developmental time course correlates well with the appearance of corticomotoneuronal projections (Kuypers 1962; Armand et al. 1994, 1996, 1997; Galea and Darian-Smith 1995). In monkeys pyramidotomized at birth, there was no appreciable difference in the development of general motor activity including running, walking and climbing. Reaching developed in the normal fashion, but the monkeys did not develop any relatively independent finger movements (Lawrence and Hopkins 1976; Galea and Darian-Smith 1997a, b). Transcranial magnetic stimulation studies showed a correlation between the maturation of the corticospinal tract and the development of relatively independent finger movements (Flament et al. 1992a, b; Olivier et al. 1997), suggesting a staggered development of corticospinal projections to forelimb and hindlimb. Cortically evoked responses in hand muscles could be recorded about 1 month earlier than those in foot muscles.

6.7.4 Development of the Human Pyramidal Tract

The development of the human corticospinal tract was studied with silver and other fibre or myelin staining techniques (Humphrey 1960; Müller and O'Rahilly 1990b; Eyre et al. 2000; Altman and Bayer 2001). The pyramidal tract reaches the level of the pyramidal decussation at the end of the embryonic period (Humphrey 1960; Müller and O'Rahilly 1990b; Fig. 6.26). After reaching the level of the pyramidal decussation at the end of the embryonic period, a rather long waiting period occurs. Pyramidal decussation is complete by 17 weeks' gestational age, and the rest of the spinal cord is invaded by 19 gestational weeks (lower thoracic cord) and 29 gestational weeks (lumbosacral cord) (Humphrey 1960; Fig. 6.27). Using GAP43 immunohistochemistry, Eyre et al. (2000) showed that by 29 gestational weeks, the corticospinal tracts are the only major tracts expressing this neuron-specific phosphoprotein in the lower cervical cord (Fig. 6.28). Following a waiting period of up to several weeks, corticospinal fibers progressively innervated the grey matter. By 35 gestational weeks, GAP43 immunoreactivity was greatly increased in the grey matter, the dorsal and ventral horns in particular. At 37 gestational weeks, when the great majority of axons expressing GAP43 appeared to derive from the corticospinal tracts, Nissl-stained motoneuron cell bodies were closely opposed by GAP43-immunoreactive varicose axons, indicating the presence of direct corticomotoneuronal projections prenatally. Some caution would be appropriate, however, since at least some of these GAP43-labelled axons may be derived from other spinal systems. At term, direct cortical projections to

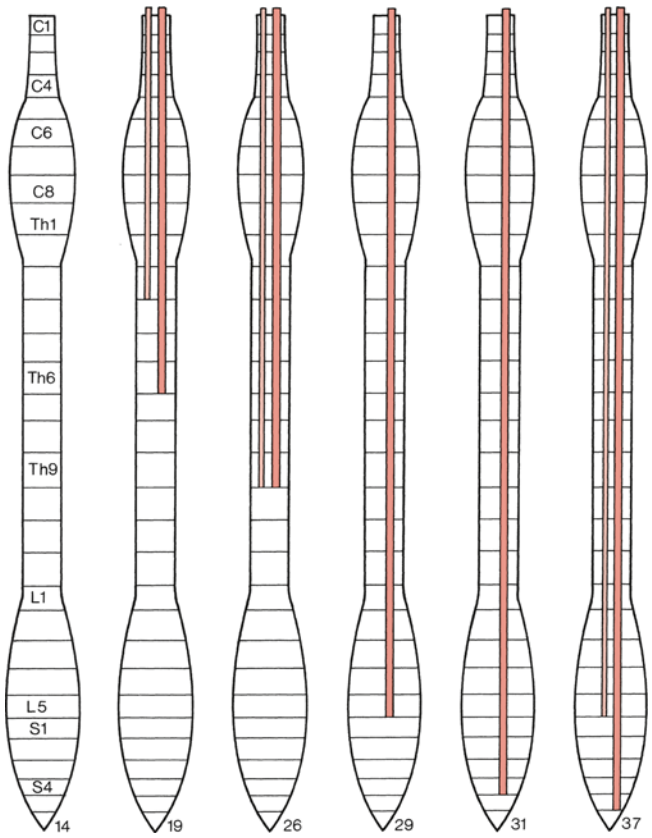

Fig. 6.27 The spinal outgrowth of the human corticospinal tracts, shown for 14, 19, 26, 29, 31 and 37 gestational weeks. The small bundles (*light red*) show the outgrowth of the anterior corticospinal tract (not found by Altman and Bayer in their fetal material of 29 and 31 weeks), whereas the larger bundles (*red*) show the outgrowth of the lateral corticospinal tract. *C1*, *C4*, *C6*, *C8*, *Th1*, *Th6*, *Th9*, *L1*, *L5*, *S1* and *S4* indicate spinal segments (After Humphrey 1960; Altman and Bayer 2001)

Ia-inhibitory interneurons were shown with electrophysiological techniques (Eyre et al. 2000, 2001).

The final pattern of the origin and termination of the corticospinal is shaped during development by the balance between projection and withdrawal of axons (Eyre 2007). In animal studies (Hicks and D'Amato 1970; Rouiller et al. 1991; O'Leary et al. 1992), unilateral inhibition of the sensorimotor cortex during development resulted in a sparse contralateral corticospinal projection and retention of a greater number of ipsilateral projections from the more active cortex. Similarly in infants with hemiplegic cerebral palsy, transcranial magnetic stimulation (TMS) of the damaged motor cortex failed to evoke responses in the contralateral paretic upper limb, whereas TMS of the undamaged ipsilateral motor cortex evoked abnormally large and short-onset responses (Staudt et al. 2002, 2004; Eyre 2007; Eyre et al. 2007; Staudt 2010; Clinical Case 6.3).

The maturation of human skilled finger movements requires a much longer period of development than in the rhesus monkey (Forssberg et al. 1991; Lacquanti et al. 2012), and is also dependent on that of the corticospinal tracts (Eyre et al. 1991; Müller et al. 1991, 1997). During the first 2 years of life, the central conduction time of responses to magnetic stimulation of the cerebral cortex rapidly declines. Adult values for central conduction times were achieved around 2–4 years of age. This extended time course is in keeping with the protracted period during which myelination of the human pyramidal tract continues. The early direct corticospinal innervation presumably permits cortical involvement in activity dependent maturation of spinal motor centres during a critical period of perinatal development. Neonates have ipsilateral corticospinal responses with shorter onsets than contralateral responses but similar thresholds and amplitudes (Eyre et al. 2000). Differential development was present from 3 months onwards so that by 18 months ipsilateral responses were smaller and had higher thresholds and longer onset latencies than contralateral responses. These data suggest that the development of the corticospinal tract may diverge between man and macaque monkeys at least in two ways: (1) the prenatal establishment of corticomotoneuronal connections in human fetuses well before the presence of relatively independent finger movements, whereas there is a close correspondence between these two events in infant monkeys; and (2) the coexistence in human neonates of fast-conducting contralateral and ipsilateral corticospinal projections which are differentially withdrawn during the postnatal period, whereas ipsilateral corticospinal projections are sparse in neonate macaques.

L1 cell adhesion molecule (L1CAM) gene mutations are associated with X-linked 'recessive' neurological syndromes characterized by spasticity of the legs. *L1CAM* knockout mice show hypoplasia of the corticospinal tract and failure of corticospinal axonal decussation and projection beyond the cervical spinal cord. In a 2-week-old male with an *L1CAM* mutation, Dobson et al. (2001) showed normal corticospinal decussation and axonal projections to lumbar spinal segments. Their data support a role for L1CAM in corticospinal tract development in hemizygous males and 'carrier' females, but do not support a critical role for L1CAM in axonal guidance of the pyramidal tract. A case of an *L1CAM* mutation is shown in Clinical Case 6.4.

Myelination of the pyramidal tract is already in progress at the level of the pyramidal decussation in a 220-mm-CRL fetus at 25 weeks of gestation (Woźniak and O'Rahilly 1982). Myelination of the pyramidal tract occurs over a protracted period (Yakovlev and Lecours 1967; Altman and Bayer 2001). In the fetal and neonatal spinal cord, in MBP or Weigert stained sections the massive lateral corticospinal tracts stand out as unstained areas in the white matter (Fig. 6.42a, b). The cranial part of the pyramidal tract is myelinated much earlier than its spinal part. Myelination of the entire corticospinal tract may be completed between 1 and 2 years of age. The MRI pattern of myelination lags

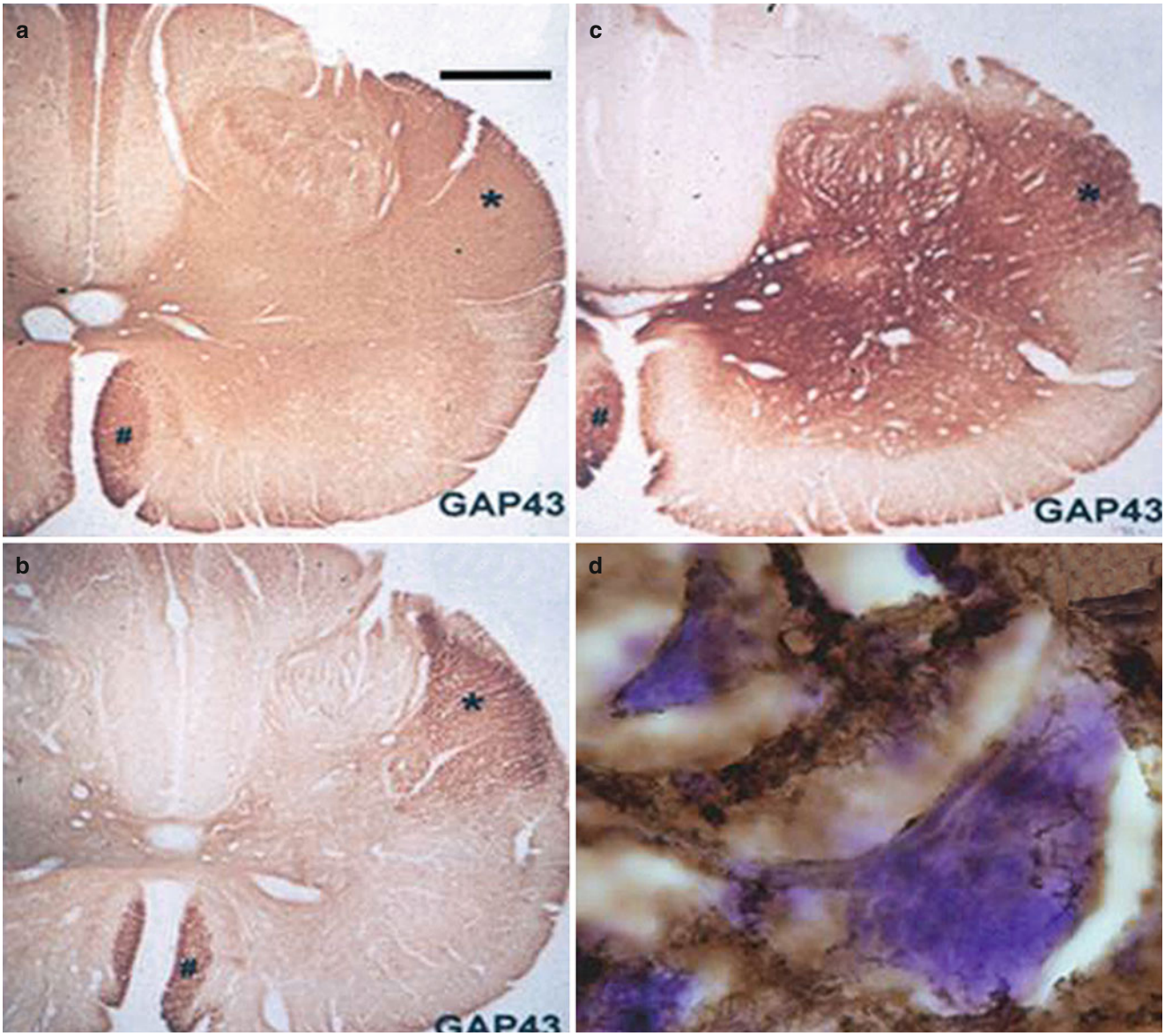

Fig. 6.28 Horizontal sections of the human spinal cord at C5-C6. The *stars* mark the lateral and anterior corticospinal tracts. (**a**) 24-weeks postconceptional age (PCA), GAP43 immunoreactivity is widespread in white and grey matter; (**b**) 27 weeks PCA, the corticospinal tracts are the only major tracts expressing GAP43, from which weaker immunoreactivity extends into the intermediate grey matter; (**c**) 31 weeks PCA, immunoreactivity is now also intense in the intermediate grey and present in the motor neuronal pools and the dorsal horn; (**d**) 35 weeks PCA, section counterstained with cresyl violet. Motoneuron cell bodies are closely apposed by GAP43 immunoreactive varicose axons (From Eyre et al. 2000; photomicrographs kindly provided by Janet Eyre, Newcastle; with permission)

several weeks behind if compared with the histological timetable, probably owing to the minimal concentration of myelin required to change the signal intensity on the MR image (van der Knaap and Valk 1995). Apart from a clear rostral-to-caudal gradient in the progression of reactive gliosis and subsequent myelination within the lateral corticospinal tract, a medial-to-lateral gradient also seems likely (Altman and Bayer 2001). Since Foerster's (1936) studies, a rather precise segmental organization of corticospinal tract fibres is thought to be present in the cervical cord (but see Brodal 1981 for critique). According to this scheme, corticospinal fibres terminating in the upper cervical cord are located most medially, and fibres for more caudal levels of the spinal cord form shells in a medial-to-lateral sequence. Myelination starts in a medial fascicle related to the cervical and thoracic cord, followed by an intermediate fascicle for the lumbar cord, and finally a lateral fascicle for the sacral cord (Altman and Bayer 2001). Myelination spreads along the entire cervical cord by 3–4 months, reaches the thoracic cord by 5–7 months, and at

10–11 months myelination is in progress in the lumbar cord. Myelination of the corticospinal tract is correlated with motor behaviour.

In recent years, several signalling pathways have been found to be crucial in mediating CNS midline crossing in vertebrates (Chap. 2). So far, only a handful of mutations leading to ***midline-crossing defects*** have been identified (Vulliemoz et al. 2005; Izzi and Charron 2011; Nugent et al. 2012; Peng and Charron 2013). The majority of the mutations identified localized to the *DCC* and *ROBO3* genes (Fig. 6.24), and are associated with congenital mirror movements and horizontal gaze palsy with progressive scoliosis. **Mirror movements** are involuntary movements occurring on one side of the body that mirror intentional movements on the contralateral side (Cincotta and Ziemann 2008; Bonnet et al. 2010; Koerte et al. 2010). They occasionally occur in normal children, but progressively diminish and rarely occur after the age of 7. ***Congenital mirror movements*** (***CMM***) is a familial disorder with autosomal dominant inheritance with incomplete penetrance. In children and adults with CMM, TMS studies showed that M1 stimulation evokes rapid motor evoked potentials (MEPs) in both contralateral and ipsilateral muscles with synchronous latencies (Cincotta et al. 2003; Cincotta and Ziemann 2008). An abnormal fast-conducting ipsilateral corticospinal tract suggests a partial failure of pyramidal decussation and a defect in the formation of the ipsilateral tract (Cincotta and Ziemann 2008; Bonnet et al. 2010). Mutations in the *DCC* gene on chromosome 18 have been identified in three families of French Canadian, Iranian and Italian descent with affected members (Srour et al. 2010; Depienne et al. 2011). Recently, two families with mutations in the *RAD51* gene were found (Depienne et al. 2012).

Horizontal gaze palsy with progressive scoliosis (***HGPPS***) is a rare autosomal recessive disorder characterized by a congenital absence of conjugate lateral eye movement as well as a progressive scoliosis which develops in early childhood (Dretakis 1970; Chap. 7). It results from axonal midline crossing defects of specific populations of neurons in the hindbrain and possibly the spinal cord. Loss-of-function mutations in the axon guidance receptor ROBO3 were found to underlie HGPPS (Jen et al. 2004). Imaging studies revealed a hindbrain malformation that correlates with failure of the corticospinal tract and the medial lemniscus to decussate in the hindbrain (Jen et al. 2004; Sicotte et al. 2006; Avadhani et al. 2010). An HGPPS patient with a *ROBO3* mutation, who suffered a stroke in the motor cortex, showed ipsilateral limb weakness and facial palsy (Ng et al. 2011), confirming an uncrossed corticospinal tract in HGPPS. It is remarkable that HGPPS patients have relatively normal gross motor, sensory and proprioceptive functions. This suggests that corticospinal axons innervate targets correctly, but on the ipsilateral rather than on the kcontralateral side.

Clinical Case 6.3. Corticospinal System Reorganization

During normal development, corticospinal projections from the motor cortex have reached the lower cervical spinal cord by 24 weeks postconceptional age (PCA), and following a waiting period of up to a few weeks, corticospinal fibres progressively innervate the grey matter (Eyre et al. 2000). There is extensive innervation of spinal neurons, including motoneurons, prior to birth. Functional monosynaptic corticomotoneuronal projections were demonstrated neurophysiologically from term, but may be present from as early as 26 weeks PCA (Eyre et al. 2000). During this period, each hemisphere initially develops bilateral projections. Ongoing development is characterized by a gradual weakening of ipsilateral projections, paralleled by strengthening of contralateral projections (Eyre et al. 2001). This normally transient existence of ipsilateral corticospinal projections provides the basis for a type of motor reorganization (Staudt et al. 2002, 2004; Eyre et al. 2007).

With transcranial magnetic stimulation (TMS), Eyre et al. (2007) characterized corticospinal tract development from each hemisphere over the first 2 years in 32 healthy children, 14 children with unilateral stroke and 25 with bilateral lesions. Three cases are shown in Fig. 6.29. Infants with unilateral lesions initially had responses after TMS of the affected cortex, which became progressively more abnormal, and seven were eventually lost. There was associated hypertrophy of the ipsilateral corticospinal axons projecting from the non-infarcted hemisphere. TMS findings soon after the stroke did not predict impairment; subsequent loss of responses and hypertrophy of ipsilateral corticospinal axons from the non-infarcted cortex predicted severe impairment at 2 years. Infants with bilateral lesions maintained responses to TMS from both hemispheres with a normal pattern of development.

This case was kindly provided by Janet Eyre (Department of Developmental Neuroscience, School of Clinical Medical Sciences, University of Newcastle, United Kingdom).

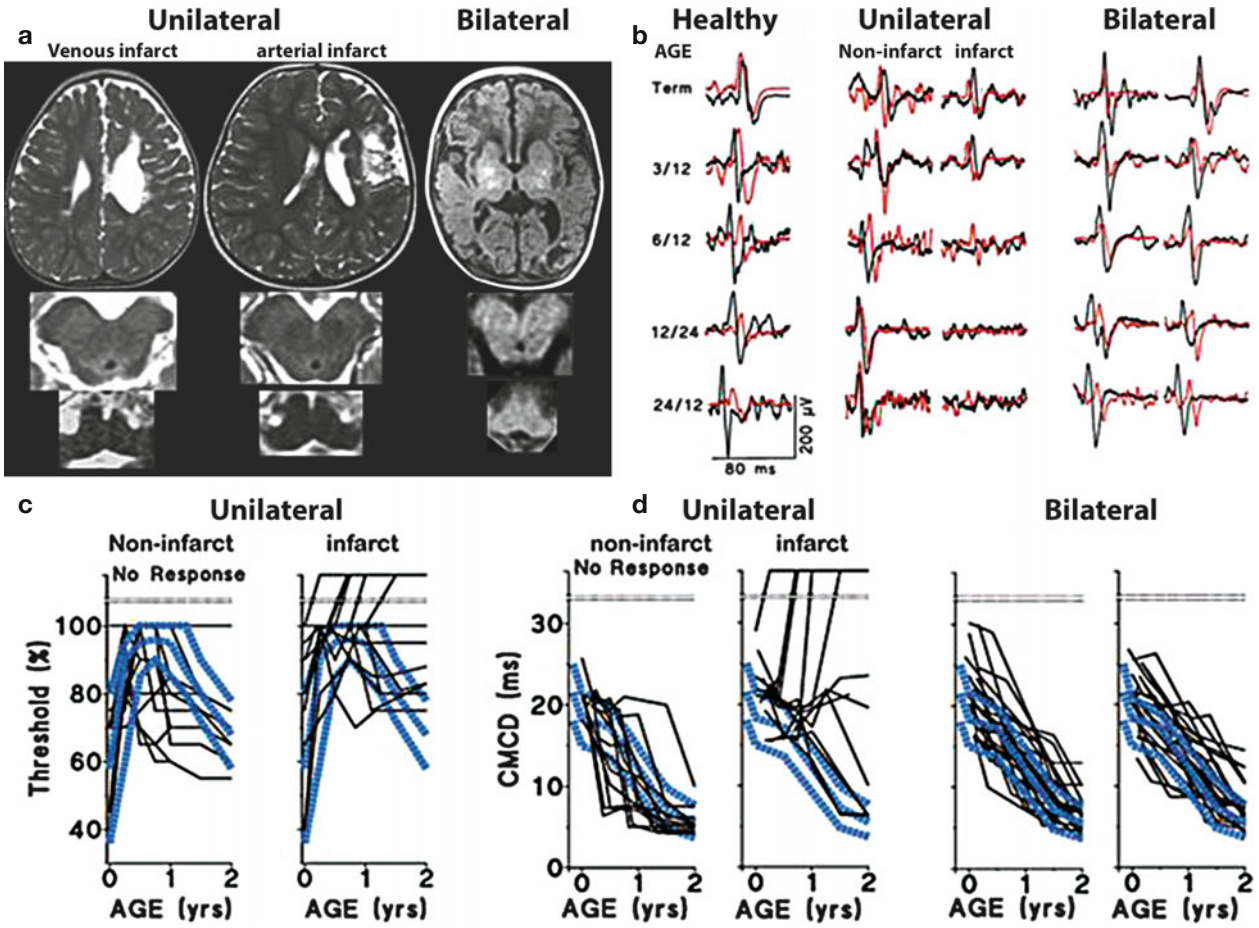

Fig. 6.29 (**a**) Axial MR scans of subjects in a longitudinal study when aged 2 years showing sections at the level of the cortex (*top*), cerebral peduncle (*middle*) and pyramid (*below*) for cases of a unilateral venous infarct after periventricular intraventricular haemorrhage, a unilateral arterial infarct in the media territory, and extensive bilateral cortical and subcortical infarcts after birth asphyxia. (**b**–**d**) Development of corticospinal projections from each hemisphere: (**b**) motor-evoked potentials (MEPs) evoked in the biceps after transcranial magnetic stimulation (TMS) of the cortex at term, 3, 6, 12 and 24 months. *Black traces* denote electromyogram (EMG) recorded from the contralateral biceps. *Red traces* denote EMG recordings from ipsilateral biceps. (**c**, **d**) The thresholds (**c**) and central motor conduction delays (CMCDs; (**d**) of MEPs evoked in the contralateral biceps after TMS of the non-infarcted and infarcted hemispheres, respectively, in the 14 subjects followed longitudinally after unilateral perinatal stroke. The CMCD of MEPS, evoked in the contralateral biceps after TMS of the right and left hemispheres in the 25 subjects with bilateral lesions, are shown at the right in (**d**). *Hashed blue lines* indicate the mean ± two standard deviations for healthy subjects, *black lines* join the results for individual subjects (From Eyre et al. 2007; kindly provided by Janet Eyre, Newcastle; with permission)

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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).

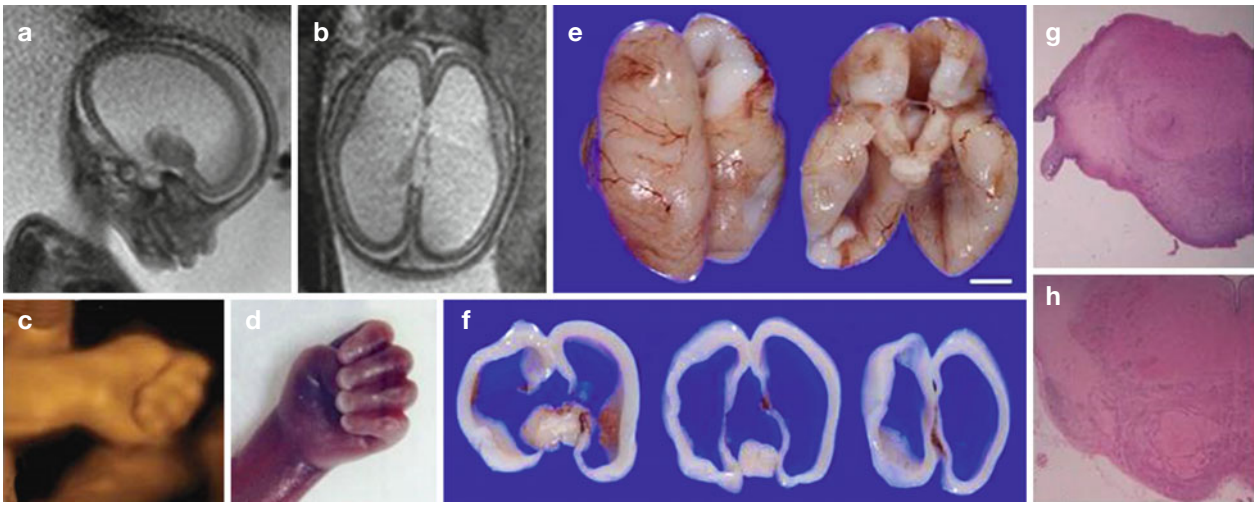

Fig. 6.30 (**a**–**d**) Fetal MRIs at the 18th week of gestation showing the extensive hydrocephalus of a L1CAM case; (**e**, **f**) 3D-ultrasound (**e**) showing the adducted thumb of the fetus, confirmed at autopsy (**f**); the cerebral hemispheres showed normal convexity (**g**); in sections (**h**), 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

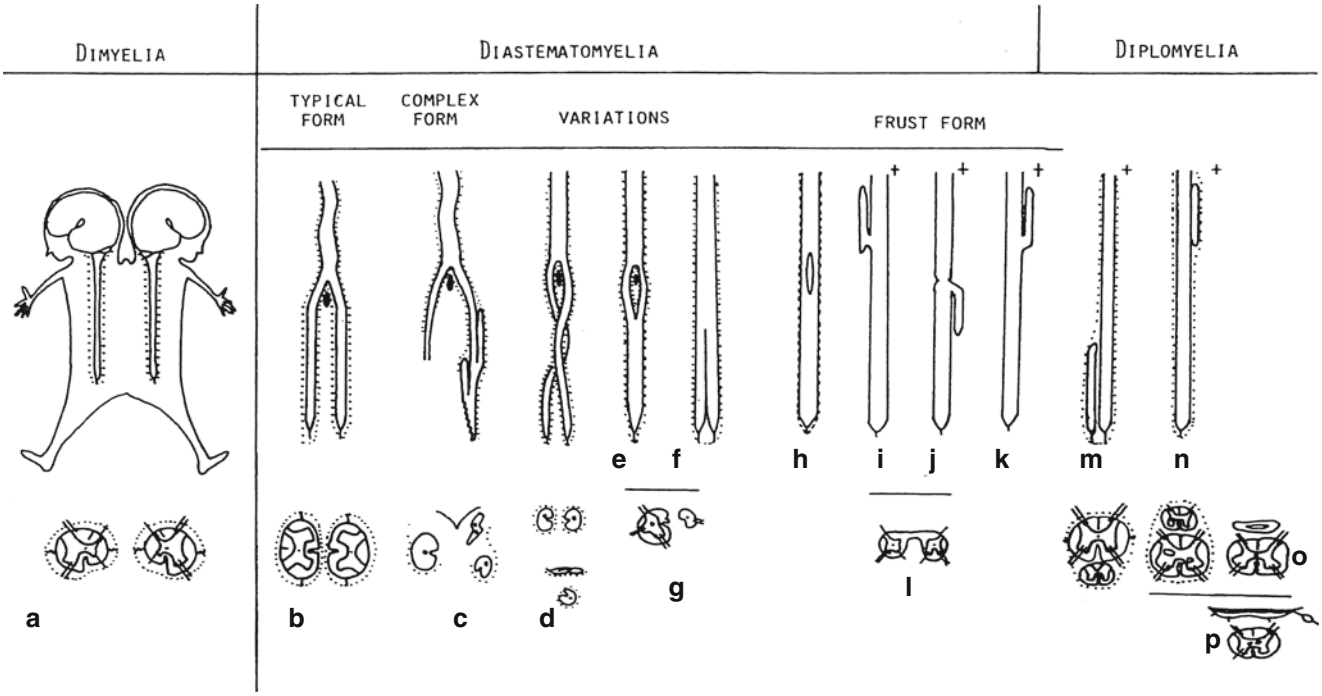

Fig. 6.31 Duplications of the spinal cord. Summary of the morphologic features of cases of dimyelia, diastematomyelia and diplomyelia: (**a**–**c**) (Hori et al. 1982); (**d**) (Rokos 1975); (**e**) (Benstead 1953); (**f**) (James and Lassman 1964); (**g**, **l**) (Emery and Lendon 1974; reverse form 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).

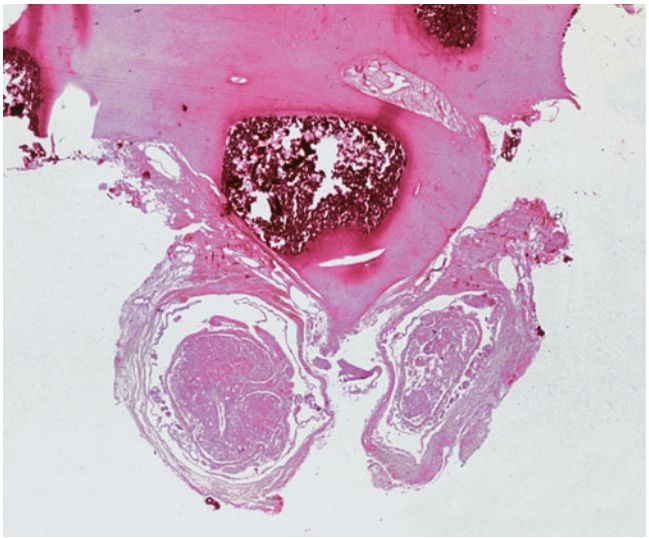

Fig. 6.32 A case of complex diastematomyelia showing a bony spur dividing the lumbar spinal cord in two parts

Clinical Case 6.5. Diplomyelia

Multiplication of the spinal cord in human embryos has occasionally been described (Fig. 6.31). Környey (1925) described an isolated dorsal accessory cervical cord associated with extensive malformations of the brain. Dominok (1962) published a case with a dorsal thoracolumbar accessory cord with rudimentary posterior roots, whereas the dorsal thoracolumbar accessory cord in Schneiderling's case (1938) was less differentiated and formed a medullary plate, but with spinal roots as well as a spinal ganglion in the subdural space. Hori et al. (1982) described a case of diplomyelia (see Case Report).

Case report. The mother, a primigravida and primipara, had an uneventful pregnancy with labour beginning at term. The newborn girl appeared unremarkable at birth and had Apgar scores of 9 at 1 min and 10 at 5 min. The following day, however, she became cyanotic, femoral pulses could not be palpated, and an echocardiogram showed left cardiac hypoplasia. She died of acute cardiac insufficiency 4 h after her first examination on the second postnatal day. At autopsy, severe hypoplasia of the left ventricle with severe endocardial fibrosis, moderate hypoplasia of the aortic arch and the ascending aorta, an open foramen ovale and a patent ductus arteriosus were found. The macroscopically normal brain weighed 376 g after fixation. Histologically it was normal, apart from heterotopic neuronal nests in the cerebellar white matter. An *accessory spinal cord* was found between the lower lumbar segment and the cauda equina ventral to the regular spinal cord (Fig. 6.33a). The accessory cord had no roots and no denticulate ligaments. For histological examination, it was, together with the regular cord, embedded in paraffin and studied in serial sections. The grey and the white matter of the accessory cord were abundant, but the posterior columns appeared hypoplastic, although well myelinated (Fig. 6.33b). The regular and the accessory spinal cords were covered by a common dura and arachnoidea. There was no separating tissue between the two cords and no bony spine in the spinal canal. The regular cord had a proper pia, but the accessory cord had only a circumscribed rudimentary pia. There was no parenchymal continuity between the two cords. In a root of the cauda equina of the regular cord at the level of the filum terminale, there was a subdural heterotopic spinal ganglion as well as several isolated preganglionic neurons in the root itself. No other anomalies were found in the regular spinal cord. Subdural heterotopic spinal ganglia were also observed in cases of an accessory cord as well as in diastematomyelia (Schneiderling 1938).

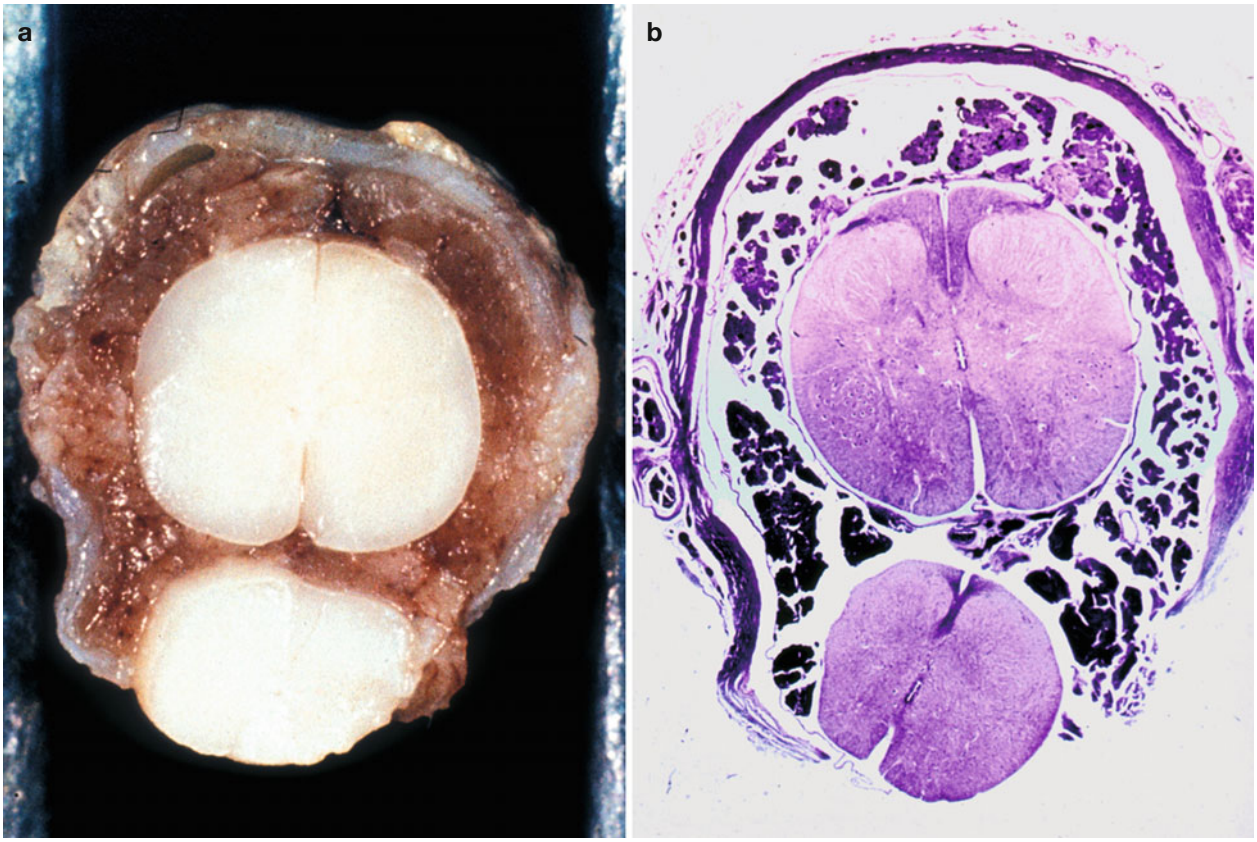

Fig. 6.33 Macroscopic (**a**) and microscopic (**b**) views of a case of diplomyelia (From Hori et al. 1982)

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6.8.3 Neurenteric Cysts

Enterogenous or ***neurogenic cysts*** are rare developmental anomalies that can be seen anywhere along the gastrointestinal tract (Veeneklaas 1952; Bentley and Smith 1960; Kumar et al. 2001; ten Donkelaar et al. 2002). They may extend into the intradural compartment, especially around the spinal cord. The latter cases are frequently associated with midline fusion abnormalities of the vertebral column. Cervical and upper thoracic segments are most often affected. Enterogenous cysts are considered to be the result of a disturbance in the interrelations between the ectoderm, the notochord and the endoderm. During its development at the end of the third embryonic week, the notochord is intimately related with endodermal cells (Fig. 6.34). If the notochord fails to detach itself from the endodermal layer, endodermal cells can be dragged forwards and upwards. This may lead to the formation of a cyst. Any adhesion between the ectoderm and the endoderm in the presomite embryo in which the two layers are in close proximity may split or divert the notochord during its caudorostral development and may give rise to an enterogenous cyst (Clinical Case 6.6).

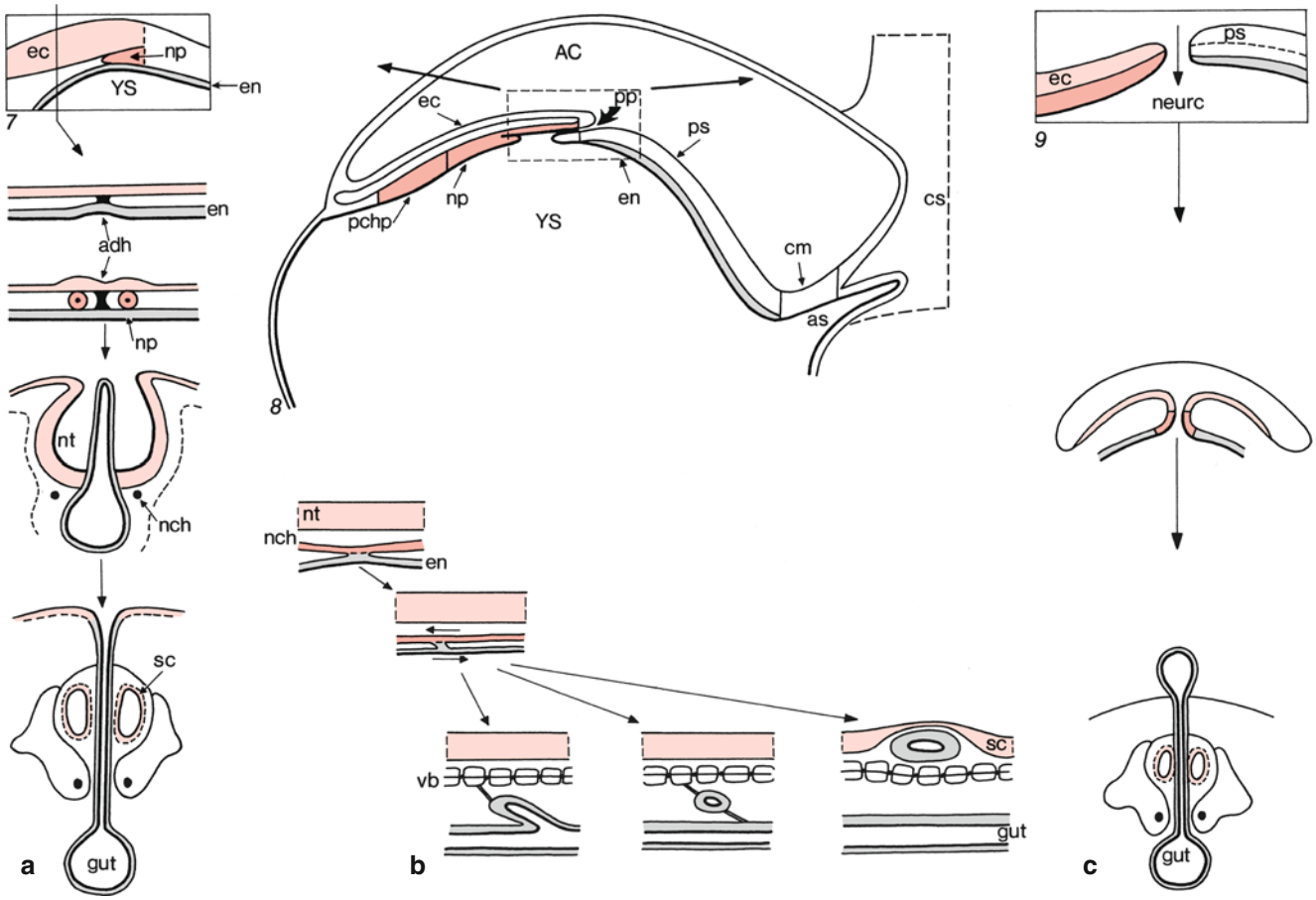

Fig. 6.34 The possible developmental history of enterogenous or neurenteric cysts and related disorders. The numbers in *italics* refer to the developmental stages shown. (**a**) An adhesion (*adh*) between the ectoderm (*ec*) and the endoderm (*en*) may lead to a split notochord syndrome. In this situation the notochordal process (*np*) will be split into two notochords (*nch*), resulting in hemivertebrae, a split neural tube (*nt*) giving rise to diastematomyelia, and various forms of enterogenous structures such as a posterior enteric fistula, dermoid cysts and dermal sinus tracts (Chap. 4). (**b**) *Top*: The development of the notochordal process into the notochord between stages 8 and 12. The neurenteric canal begins at the primitive pit (*pp*) and opens into the yolk sac (*YS*). *Bottom*: the possible mechanism of development of an enterogenous cyst. (**c**) Persistence of the neurenteric canal (*neurc*) results in the split notochord syndrome with hemivertebrae, a double spinal cord and a dorsal enteric cyst. *AC* amniotic cavity, *as* allantois, *cm* cloacal membrane, *cs* connecting stalk, *pchp* prechordal plate, *ps* primitive streak, *sc* spinal cord, *vb* vertebral bodies (After Bremer 1952; Bentley and Smith 1960; Skandalakis and Gray 1994; O'Rahilly and Müller 2001; ten Donkelaar et al. 2002)

Clinical Case 6.6. A Spinal Intradural Enterogenous Cyst

Case report. In a newborn girl, the second child of nonconsanguineous parents, a large intradural extramedullary cystic lesion was found that severely compressed the spinal cord (ten Donkelaar et al. 2002). Pregnancy was complicated by gestational diabetes. The mother noted long periods of strange, rhythmic movements of the fetus during the last months of pregnancy. Labour was induced at a gestational age of 38 weeks. Delivery was uncomplicated with Apgar scores of 7 and 8 after 1 and 5 min, respectively. The birth weight was 3,525 g. Physical examination showed severe contractures of all extremities, and a midline area of abnormal skin on the back with a maximum diameter of 2 cm. Muscle tone was elevated in both arms and legs. The biceps and triceps tendon reflexes were absent, whereas in the legs pathological hyperreflexia was found. Spontaneous micturition was absent. During the first hours of life respiratory insufficiency gradually developed, and necessitated artificial ventilation during the first day of life. MRI of the spine showed a large solitary mass, extending from C4 to T2 (Fig. 6.35). The mass was homogeneous and hyperintense on T2-weighted images. There was severe compression and dorsal displacement of the spinal cord, and extensive hydrocephalus. An extensive spina bifida was found in the lower part of the cervical vertebral column with

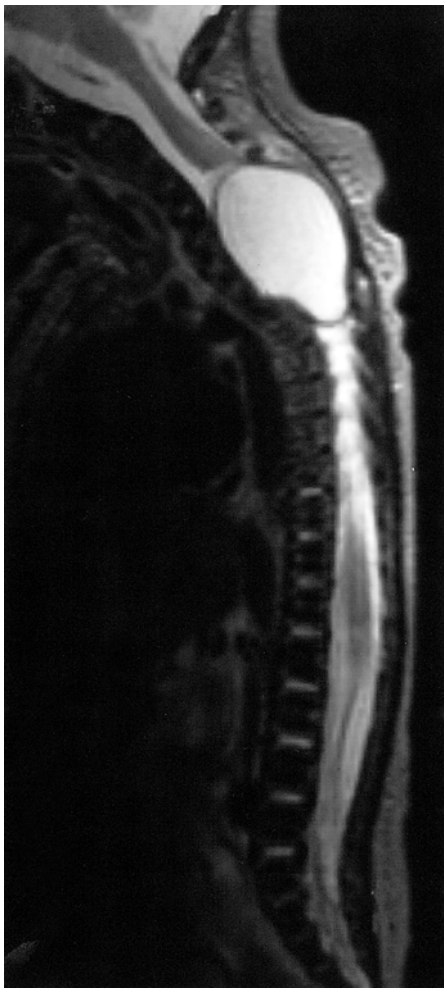

Fig. 6.35 Sagittal T2 MRI showing the extent of the intradural cyst with severe spinal cord depression. Note the malformed vertebral bodies from C7 to T2 (From ten Donkelaar et al. 2002)

almost completely absent spinal arcs. The corpora of the vertebrae C7-T2 were somewhat malformed, but not split anywhere. Neurosurgical exploration revealed a tract from the atypical cutis to the muscular fascia and a large intradural, extramedullary cystic lesion, severely compressing the spinal cord. A biopsy was taken from the cystic wall. The clinical course was characterized by a slow progression of the respiratory failure due to severe myelopathy. The child died on the 19th day of life.

At autopsy, the cervicothoracic part of the spinal canal and dural sac were found to be widened, and largely filled with an intradural mass with a smooth surface (Fig. 6.36a, b). The adjacent parts of the spinal cord were dorsally displaced, compressed and severely atrophic. The tumour with a size of 2 cm × 1.8 cm × 1 cm had a concentric architecture, with microscopically mucosa at the inner surface of the wall, surrounded by fibrous, submucosal tissue and a prominent layer of smooth muscle tissue, the latter consistent with muscularis propria (Fig. 6.36c–g). In both submucosa and muscularis propria dispersed clusters of ganglion cells were present. The gastrointestinal and respiratory tracts were completely normal. The large, intradural cyst appeared to be of mixed origin, and consisted of gastric, oesophageal and respiratory components. The presence of a bona fide muscularis propria suggests that the cyst is a duplication of the gastrointestinal tract, displaced into the spinal canal.

Hypotheses on the pathogenetic mechanism by which enterogenous cysts develop all focus on early embryogenesis (Fig. 6.34). They are formed by a disturbance in the interrelations between the notochord, ectoderm and endoderm. During the outgrowth of the notochordal process, any adhesion between the ectoderm and the endoderm may split or divert the notochord during its caudorostral development (Fig. 6.34a), resulting in malformations known as the split notochord syndrome (Feller and Sternberg 1929; Bentley and Smith 1960; Pang et al. 1992), in extreme form characterized by the presence of a double spinal cord. Such adhesions may give rise to an accessory neurenteric canal around which an endomesenchymal tract condenses that bisects the developing notochord and causes formation of two hemineural plates. It is conceivable that a less severe malformation may lead to the presence of an enterogenous cyst ventral to the spinal cord with subsequent fusion of split vertebrae. The presence of a tract from the atypical cutis to the muscular fascia may support such an explanation. Alternatively, persistence of the transient neurenteric canal may give rise to the split notochord syndrome (Bremer 1952; O'Rahilly and Müller 2001; Fig. 6.34c). Another mechanism for the formation of dorsal enterogenous cysts may lie in the early, intimate relationship of the notochordal process and the endoderm (Fig. 6.34b). Normally, the notochord separates from the endoderm, and a normal gut and vertebral column result. However, if during this process a portion of the notochord and the developing gut fail to separate, differences in growth between the two structures will put a cord of endodermal cells from the roof of the gut, leading to a diverticulum or cyst (Skandalakis and Gray 1994).

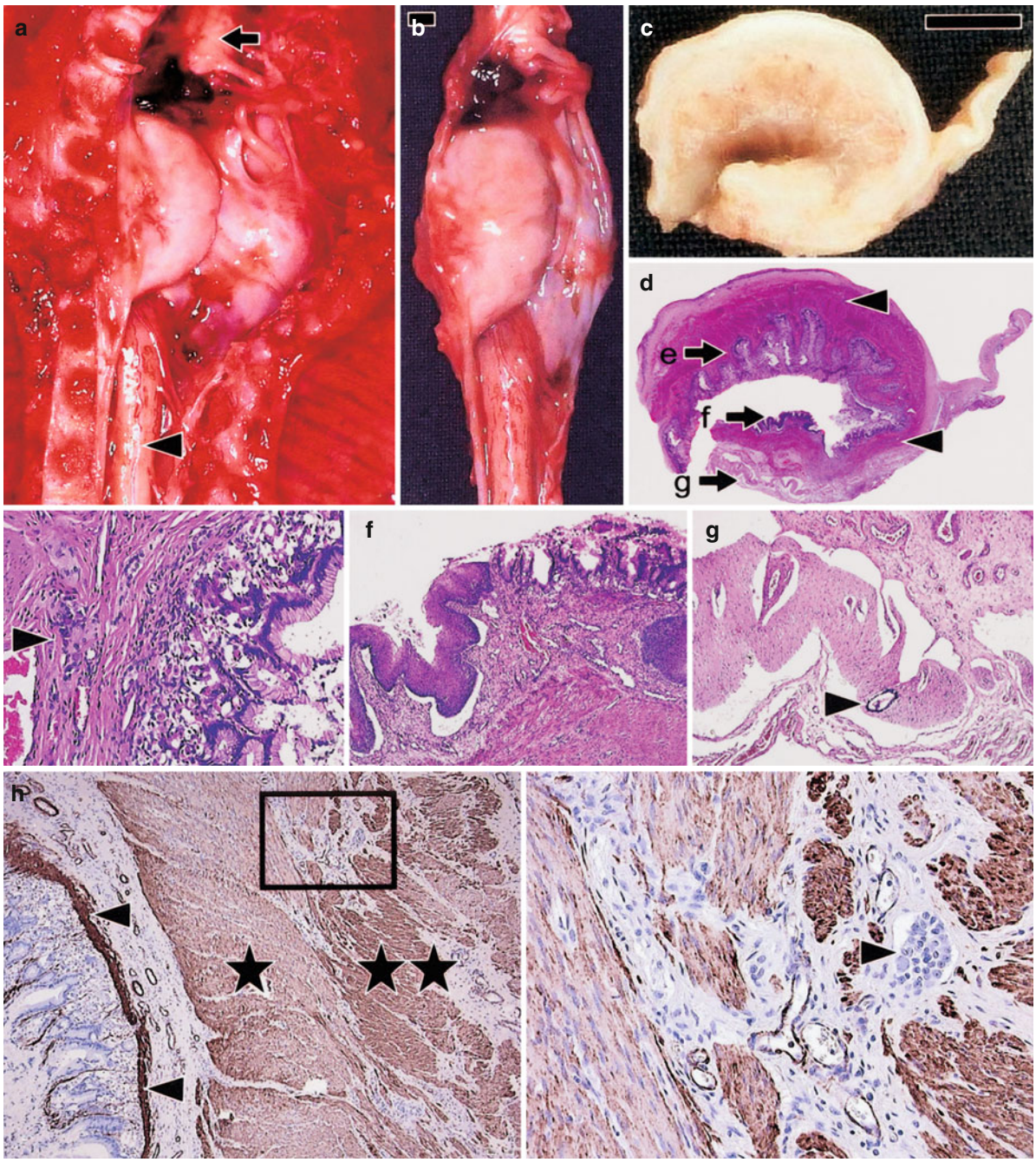

Fig. 6.36 Macroscopical (**a**–**c**) and microscopical (**d**–**i**) neuropathological findings in a spinal intradural enterogenous cyst. (**a**, **b**) The in situ position of the cyst and more cranial (*arrow*) and caudal (*arrowhead*) parts of the spinal cord, in (**a**) after removal of the vertebral bodies and opening of the dural sac, and in (**b**) after removal of the dural sac plus contents from the spinal canal. (**c**, **d**) A cross-section of the intradural lesion after fixation (**c**) and in a haematoxylin-eosin-stained slice (**d**). Note the concentric architecture of the lesion with mucosa at the inner surface of the wall, and a prominent surrounding layer of smooth muscle tissue (*arrowheads*) resembling muscularis propria. On the *right*, the transition to the dural sac is seen. (**e**–**g**) Higher magnifications of the areas indicated in (**d**) by *arrows* (haematoxylin-eosin staining). Note that the mucosa in (**e**) resembles fundus-type gastric mucosa with mucus-producing columnar cells in the superficial part and parietal cells in the deeper portions of the glands. The *arrowhead* in (**e**) indicates a cluster of ganglion cells in the submucosa. In (**f**), a transition between mucus-producing mucosa and non-keratizing squamous epithelium is seen, the latter resembling the mucosa of the esophagus; In (**g**), compressed neuroglial tissue in the periphery of the dorsal part of the lesion is seen; the *arrowhead* indicates the central canal with ependymal lining. (**h**) An α-smooth muscle actin staining accentuates the muscularis mucosa (*arrowheads*) and the internal and external layer of the muscularis propria (*one* and *two asterisks*, respectively) in the wall of the cystic lesion. The area in the *rectangle* in (**h**) is shown at higher magnification in (**i**), and contains a cluster of ganglion cells, consistent with a plexus myentericus. *Bars* in (**b**, **c**) 0.5 cm; magnification in (**e**–**g**) ×200, in (**h**) ×50 (From ten Donkelaar et al. 2002)

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6.8.4 Syringomyelia

The term ***syringomyelia*** means tubular cavitation of the spinal cord extending over several segments (Fig. 6.37). Cavities in the medulla (***syringobulbia***) are often associated with syringomyelia. Spiller (1906) described a case of syringomyelia, extending from the sacral region of the spinal cord through the medulla oblongata, the right side of the pons and the right cerebral peduncle to the upper part of the right internal capsule. About 90 % of patients with idiopathic syringomyelia have a Chiari I malformation (Sherman et al. 1986; Harding and Copp 1997). Clinically, the disorder usually does not start before the second decade and is slowly progressive. The lesion interrupts the spinothalamic fibres as they cross the midline in the anterior white commissure just below the central canal (Fig. 6.37b). Usually, syringomyelia

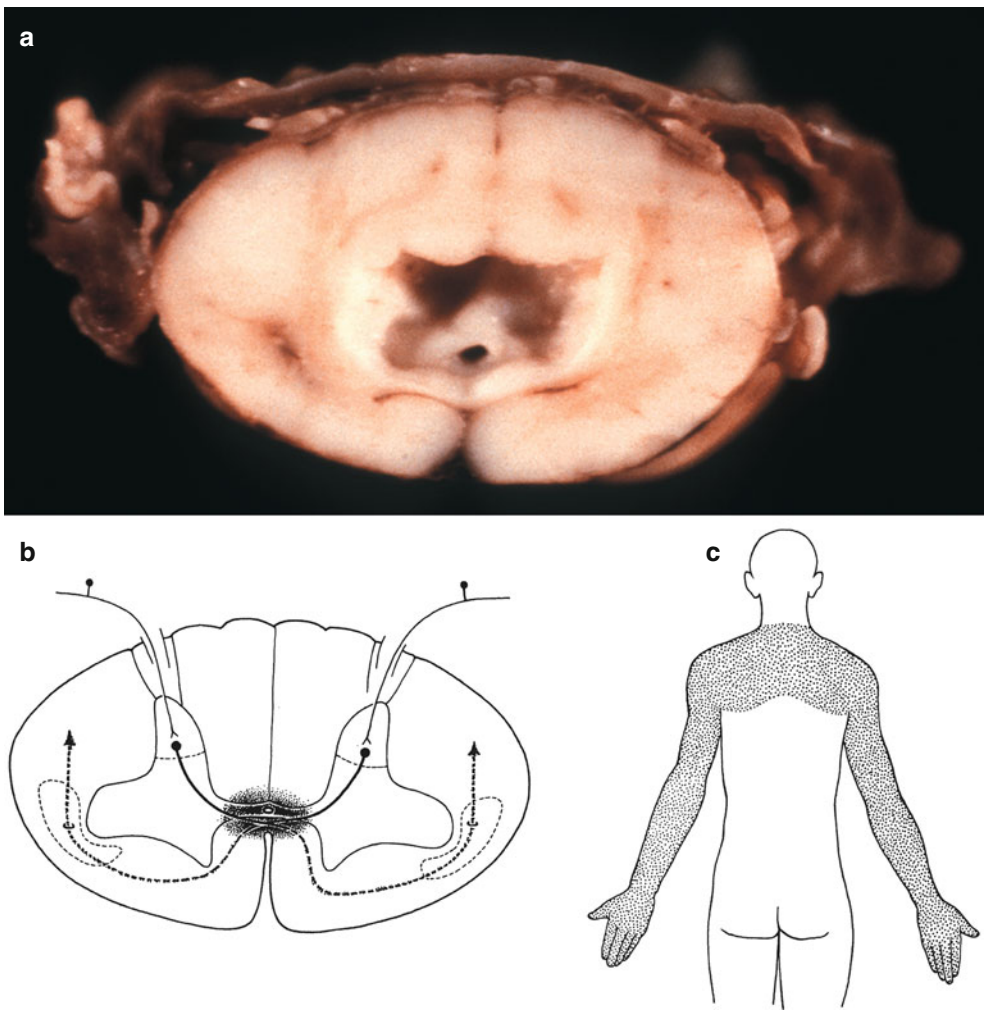

Fig. 6.37 (**a**) Syringomyelia observed in a 13-year-old girl with tuberous sclerosis; (**b**) the lesion interrupts spinothalamic fibres, leading to a cape-like distribution of pain and temperature deficit (**c**)

occurs in the lower cervical region and causes a cape-like distribution of pain and temperature deficit in the cervical and upper thoracic region.

6.8.5 Abnormal Course or Absence of Fibre Tracts

An ***abnormal course*** of the ***posterior columns*** is rare (Hori 1988b; Fig. 6.38). More common is a deviated longitudinal posterior septum, resulting in a J-form deviation of the posterior septum (Hori 1983, 1998; Parkinson and del Bigio 1996). Rudimentary development of the dorsal roots and of the posterior columns are rare malformations (Op de Coul and Slooff 1975; Kirkland 1979; Friede 1989; Vogel et al. 1990). In a 12-year-old boy with a familial insensitivity to pain, absence of small DRG cells, lack of small dorsal root fibres, absence of Lissauer's tract and reduction in size of the spinal tract of the trigeminal nerve were described (Swanson et al. 1965). Friede (1989) described ***aplasia*** of the ***posterior columns*** in a 3-day-old boy, born severely hypotonic and areflexic after Caesarean section at term to a white mother. The pregnancy was complicated by first trimester bleeding. There were three normal girls, one miscarriage and one brother who had also been areflexic and floppy and died at the age of 1 week, but no autopsy was performed. In the case reported, some craniofacial anomalies (low-set ears, mandibular hypoplasia) and hepatosplenomegaly were observed. Spontaneous movements were normal. The infant died on the third day from massive pulmonary haemorrhage. No gross anomalies of the CNS were found. Microscopic examination of the spinal cord showed an extreme degree of hypoplasia of the gracile and cuneate fasciculi and lifting up of the dorsal horns so that they nearly touched each other. Only thin vestiges of dorsal roots were seen, but the ventral roots were normal. Vogel et al. (1990) reported a case of a male infant with arthrogryposis multiplex congenita who survived for 19 weeks after birth at 36 weeks' gestational age. Severe hypoplasia of the dorsal roots and posterior columns was found.

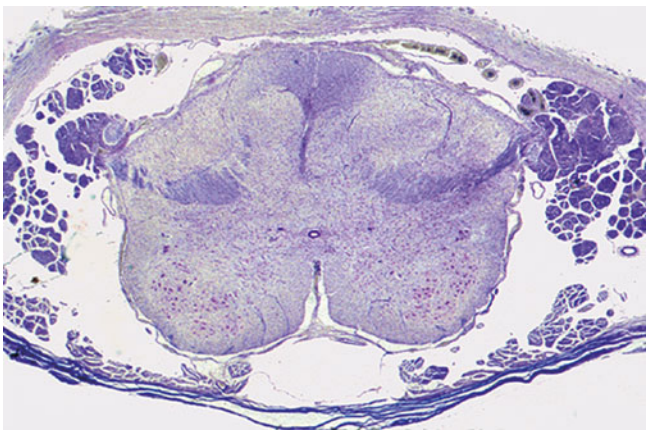

Fig. 6.38 Abnormal course of the posterior roots, entering the spinal cord lateral to the posterior horn (From Hori 1988b)

Abnormal course or even ***absence*** of the ***pyramidal tracts*** is also rare but is more common than anomalies of the ascending systems. Several variations in the funicular trajectory of the human pyramidal tract have been described in otherwise normally developed cases (Figs. 6.39 and 6.42), the most obvious being those with uncrossed pyramidal tracts (Flechsig 1876; Mestrom 1911; Kramer 1949; Verhaart and Kramer 1952; Nathan and Smith 1955; Nyberg-Hansen and Rinvik 1963; Yakovlev and Rakic 1966; Nathan et al. 1990; ten Donkelaar et al. 2004). Various ***aberrant pyramidal tract bundles*** have been described which are usually asymptomatic. The most common are the *pes lemnisci* bundles, two fibre bundles which descend partly within the cerebral peduncle and partly in the region of the medial lemniscus (Dejerine 1901; Kuypers 1958; Lankamp 1967; Verhaart 1935, 1970). The medial or superficial pes lemnisci leaves the medial part of the cerebral peduncle to descend through the medial lemniscus into the medulla, whereas a lateral or deep pes lemnisci detaches itself from the dorsal part of the cerebral peduncle, and descends in or near the medial

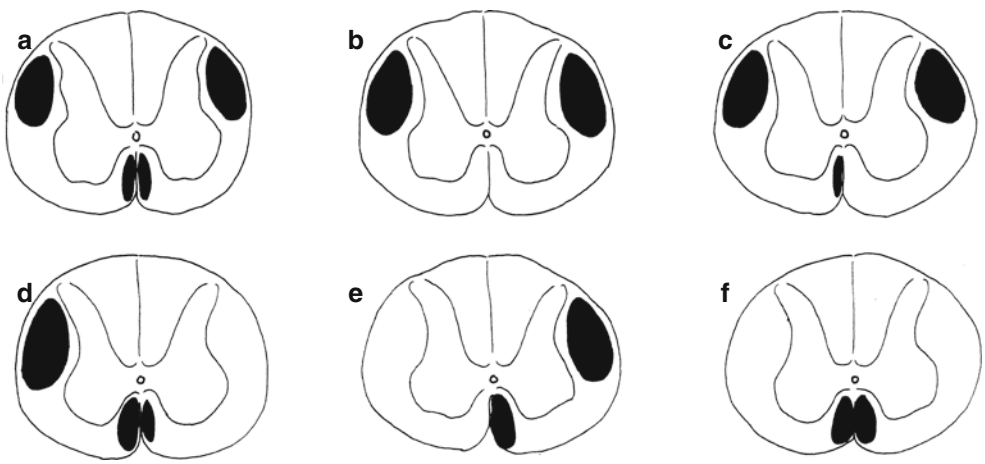

Fig. 6.39 The possible variations of the decussation of the pyramidal tracts. The following percentages refer to data by Yakovlev and Rakic (1966): (**a**) the common pattern of partial decussation (66.9 %); (**b**) complete decussation (16.2 %); (**c**) complete crossing of one pyramidal tract (13.9 %); (**d**) complete non-decussation of one pyramid (After Norman et al. 1995); (**e**) unilateral absence of pyramidal tracts (one case); (**f**) uncrossed pyramidal tracts (2.3 %) (After Mestrom 1911)

lemniscus. Corticospinal fibres may leave the pyramidal tract at the pontine level and descend lateral to the inferior olive into the ipsilateral anterolateral funiculus (Barnes 1901; Winkler 1926). Hoche (1897a, b) described a bundle of fibres leaving the pyramidal tract at the level of the VIIth cranial nerve, crossing the midline to join the contralateral pyramidal tract. Frequently, a bundle of Pick occurs (Pick 1890; Verhaart 1934). This bundle consists of recurrent pyramidal tract fibres, which after decussating in the lower medulla ascend in the bulbar lateral tegmental field (Kuypers 1958). Moreover, a recurrent circumolivary pyramidal bundle may occur (Swank 1934), a portion of which may descend as an anterolateral pyramidal tract as far as the lumbar level. In some cases a bundle of pyramidal fibres may pass from the decussation into the posterior columns (Bumke 1907; Roessmann and Hori 1985), a trajectory similar to that found in marsupials and rodents. Another rare anomaly is the presence of a superficially placed lateral corticospinal tract (Kramer 1949; Verhaart and Kramer 1952; Friede 1989). The functional significance of such aberrant bundles remains obscure.

Yakovlev and Rakic (1966) studied the spinal cord of fetuses and neonates with the Loyez technique for staining myelin sheaths. The unmyelinated pyramidal tracts could be followed as unstained bundles in their course through the medulla and the spinal cord. In 66.9 % of their cases there was partial decussation of the pyramidal tracts, leading to a larger crossed and a smaller uncrossed pyramidal tract on both sides (Figs. 6.39a and 6.40a). Complete decussation of both pyramids with absence of both anterior pyramidal tracts was found in 16.2 % (Fig. 6.39b). In the next most common pattern (13.9 %), one pyramidal tract crossed completely (Figs. 6.39c and 6.40b). A complete decussation of the left pyramidal tract occurred six times more often than a complete decussation of the right pyramid. Complete non-decussation of one pyramid was observed by Norman et al. (1995); Fig. 6.39d. In one specimen the lateral and anterior pyramidal tracts were absent on the side of the completely crossed pyramid (Fig. 6.39e). Complete absence of decussating bundles, leading to the absence of both lateral pyramidal tracts was found in three specimens (2.3 %; Fig. 6.39f). In more than two thirds of their specimens, the fibres of the left pyramid crossed to the right side of the spinal cord at higher, more cranial levels in the decussation than the fibres of the right pyramid. Moreover, more fibres of the left pyramid decussated than of the right pyramid, whereas more fibres of the right pyramid than of the left one remained uncrossed (Nathan et al. 1990). The resulting greater number of corticospinal fibres on the right side of the spinal cord appears to be unrelated to handedness (Kertesz and Geschwind 1971).

Owing to its long, protracted development, malformations of the pyramidal tract may occur over almost the entire prenatal period, the most obvious of which is complete ***absence*** of the ***pyramidal tracts***. The corticospinal tracts are most easily accessed in a transverse section of the medulla, where they form the pyramids. ***Aplasia*** of the pyramidal tracts is characterized by the absence of the pyramids. Bilateral absence of the pyramidal tracts is usual in anencephaly and holoprosencephaly. It also occurs in many cases of antenatal and perinatal destructive lesions such as porencephaly and hydranencephaly, in X-linked congenital aqueduct stenosis, in microcephaly, and it may occur in neuronal migration disorders of the cerebral cortex (Chow et al. 1985; Friede 1989; Norman et al. 1995; ten Donkelaar et al. 1999, 2004; Fig. 6.40c–e; Clinical Cases 6.4 and 6.7). Uncommonly large pyramids were found in three cases of cerebellar hypoplasia (Anton 1922). Bilateral ***corticospinal tract hypertrophy*** was found in the X-linked form of Kallmann syndrome (Krams et al. 1999). Unilateral hypertrophy of the pyramidal tract is uncommon, and is usually associated with an early destructive lesion in the contralateral hemisphere (Dejerine and Dejerine 1902; Verhaart 1950; Friede 1989). It may also occur in hemimegalencephaly with its obvious asymmetry of the pyramids (Dambska et al. 1984; Robain et al. 1988). Malformations of the pyramidal tract due to secondarily acquired injury are discussed in Chap. 10.

Anomalies of the ***decussation*** of the ***pyramidal tract*** are mostly non-specific, coincidental anomalies (Luhan 1959; Roessmann and Hori 1985; Vogel et al. 1990; Norman et al. 1995), but are frequently found in posterior fossa malformations such as occipital encephaloceles (Verhaart and Kramer 1952), the Dandy-Walker malformation (D'Agostino et al. 1963; Lagger 1979; Janzer and Friede 1982), Joubert syndrome (Friede and Boltshauser 1978; Yachnis and Rorke 1999; ten Donkelaar et al. 2000), in trisomy 18 (Miyata et al. 2006; Clinical Case 6.8), in *ROBO3* mutations (Sect. 6.7.4) and in cases with extensive malformations of the brain stem such as in Möbius syndrome (Chap. 7).

Clinical Case 6.7. Absence of the Pyramidal Tracts

Owing to its long, protracted development, malformations of the pyramidal tracts may occur over almost the entire prenatal period, the most obvious of which is complete *absence* of the *pyramidal tracts*. The corticospinal tracts are most easily accessed in a transverse section of the medulla, where they form the pyramids. *Aplasia* of the pyramidal tracts is characterized by the absence of the pyramids. The olivary nuclei abut the ventral surface of the medulla, covered by a thin layer of marginal glia. Examples of aplasia and secondary malformations of the pyramidal tract are shown in cases of an extreme, familiar form of microcephaly, holoprosencephaly and porencephaly in Figs. 6.40, 6.41, and 6.42.

Bilateral absence of the pyramidal tracts is usual in anencephaly and holoprosencephaly. It also occurs in many cases of antenatal and perinatal destructive lesions such as porencephaly and hydranencephaly, in X-linked congenital aqueduct stenosis, in microcephaly, and it may occur in neuronal migration disorders (ten Donkelaar et al. 2004). Chow et al. (1985) found bilateral absence of the pyramids in 0.7 % of 2,850 autopsies carried out at the Royal Children's Hospital in Melbourne (Australia). They found a strong association with X-linked congenital aqueduct stenosis. X-linked hydrocephalus was first

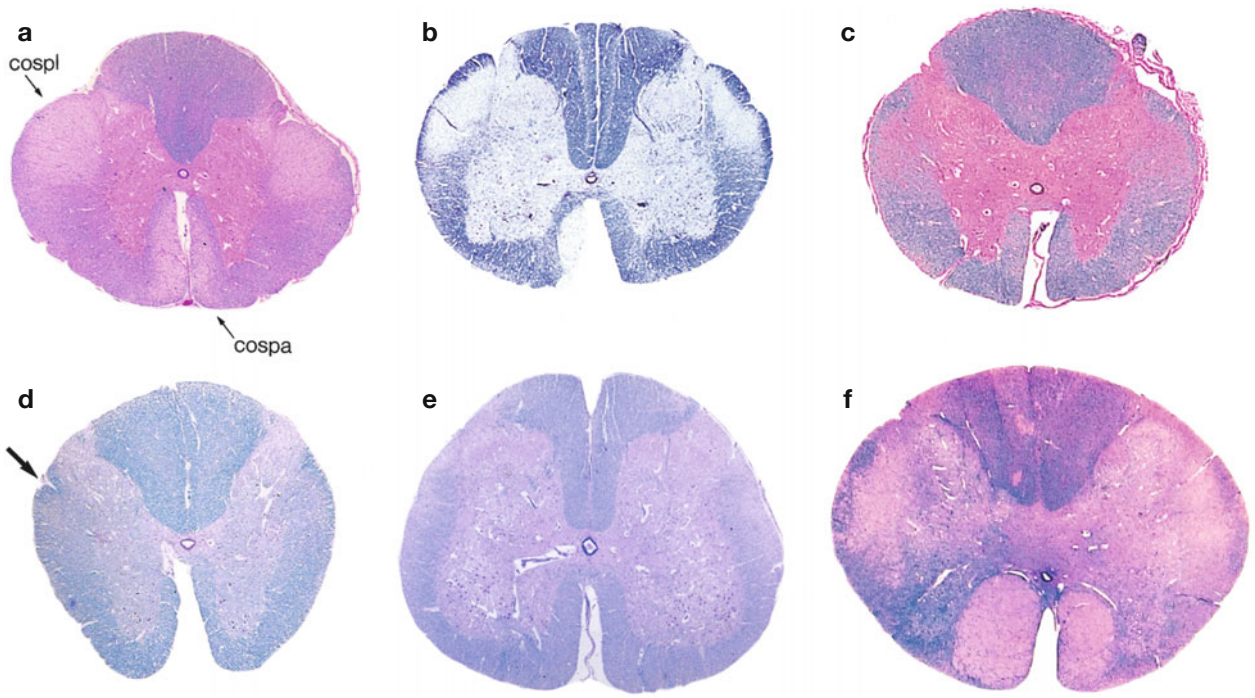

Fig. 6.40 Microscopy of the pyramidal tracts at the spinal level. In a neonatal control case (**a**), the corticospinal tracts stand out in the thoracic cord as unstained pathways. Unilateral crossing of one pyramid is shown in (**b**). Absence of the corticospinal tracts is shown for (**c**) X-linked hydrocephalus (thoracic cord), (**d**) a microcephaly case (thoracic spinal cord) - note the abnormal sulcus just below the dorsal horn (*arrow*) – and (**e**) holoprosencephaly (lumbar cord). (**f**) Non-decussation of the pyramidal tracts for a severe, lethal form of Möbius syndrome (cervical cord). *cospa* anterior corticospinal tract, *cospl* lateral corticospinal tract

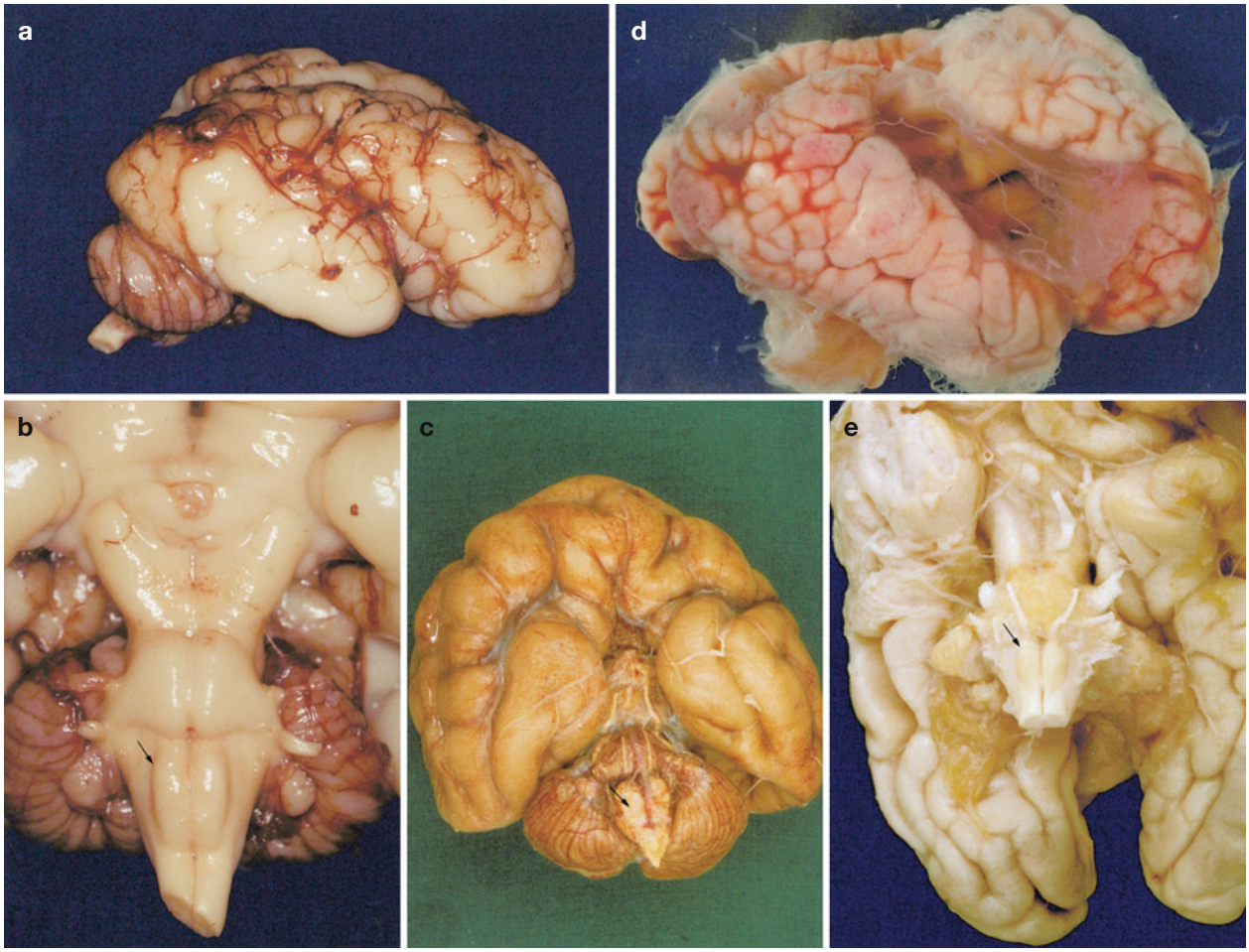

Fig. 6.41 Macroscopy of some cases with malformations involving the pyramidal tracts: (**a**, **b**) lateral and basal views of the brain in extreme, familial case of microcephaly (From ten Donkelaar et al. 1999); (**c**) basal view of the brain of a patient with holoprosencephaly; (**d**, **e**) lateral and basal views of a case of porencephaly. Note the medially located inferior olives in all cases (*small arrows*)

described by Bickers and Adams (1949) in a British family with several male sibs that died at birth from congenital hydrocephalus due to aqueduct stenosis. The discovery that *L1CAM* mutations may lead to an X-linked recessive disorder with manifestations including hydrocephalus, adducted thumbs, spastic hemiplegia, hypoplasia or agenesis of the corpus callosum and mental retardation led to a steadily increasing list of familiar and isolated cases. Since the first mutation report (Rosenthal et al. 1992), more than 100 families and isolated cases with *L1CAM* mutations have been described (Fransen et al. 1997; Finckh et al. 2000). Previously described disorders such as X-linked hydrocephalus, MASA (mental retardation, adducted thumbs, spastic paraparesis, agenesis of the corpus callosum) syndrome, X-linked agenesis of the corpus callosum and spastic paraplagia type 1 repres phenotypic variants of *L1CAM* mutations. In a screening study of 153 cases with prenatally or clinically suspected X-chromosomal hydrocephalus, Finckh et al. (2000) found a mutation detection rate of 74.2 % for patients with at least two additional cases in the family, but only 16 mutations in the 102 cases with negative family history (15.7 % detection rate). In a 2-week-old male neonate with an *L1CAM* mutation, Dobson et al. (2001) found normal pyramidal decussation and axonal projections to the spinal cord.

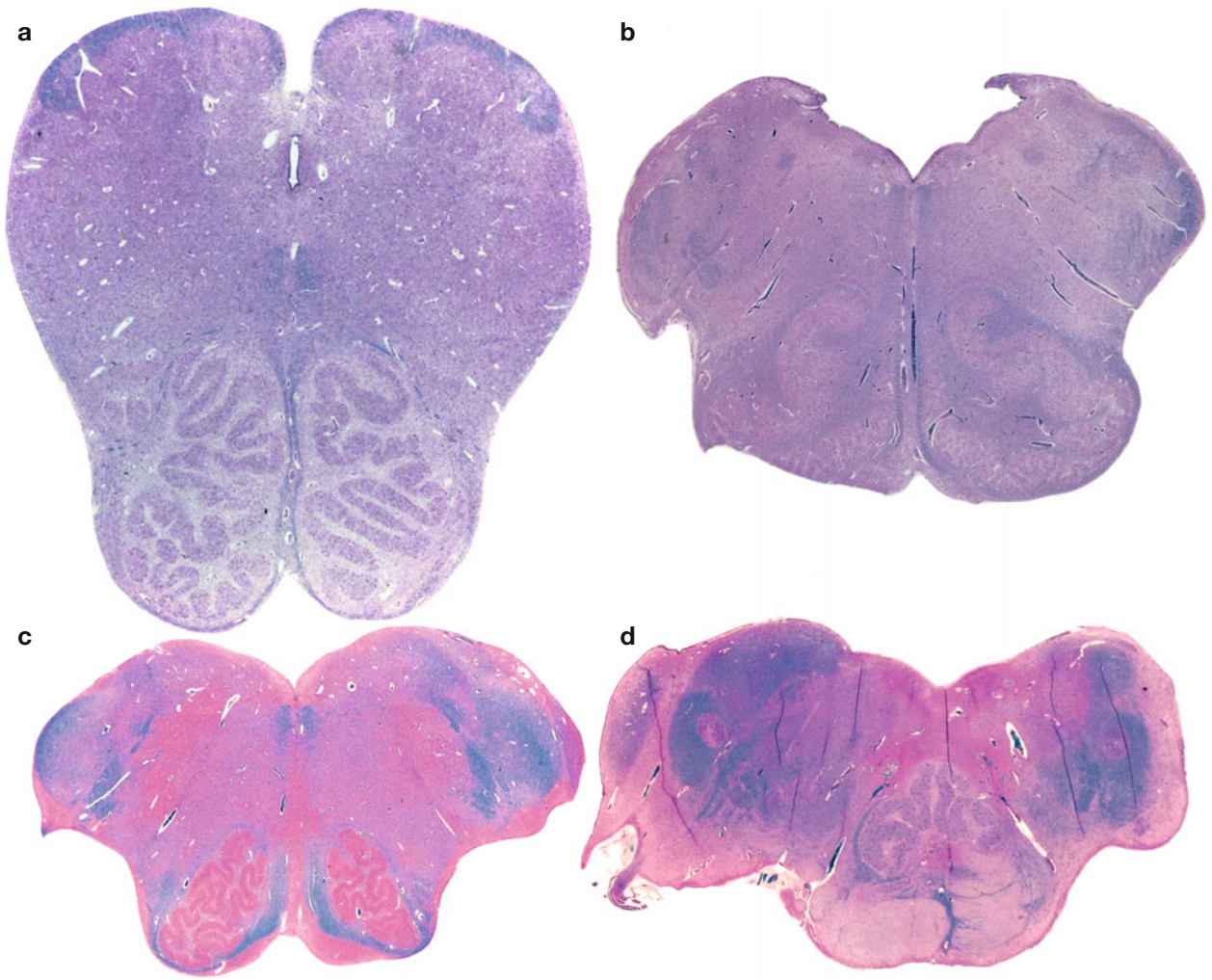

Fig. 6.42 Microscopy of the pyramidal tracts at the medullary level. Absence of the pyramids is shown for (**a**) an extreme, familial case of microcephaly (From ten Donkelaar et al. 1999), (**b**) holoprosencephaly and (**c**) X-linked hydrocephalus. (**d**) Brain stem malformations including medial inferior olives above malformed pyramids, possibly leading to non-decussation of the pyramidal tracts (Fig. 6.40f) for a severe, lethal form of Möbius syndrome

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Clinical Case 6.8. Anomaly of Decussation of the Pyramidal Tract in Trisomy 18

Miyata et al. (2006, 2014) examined eight cases of autopsied fetuses with trisomy 18 (Edwards syndrome), ranging in age from 16 to 39 weeks of gestation, including two females and six males. All cases had been diagnosed with FISH analysis of amniotic fluid and specimens were obtained within 24 h after death following therapeutic, legal or spontaneous abortions. Five of the seven cases showed incomplete pyramidal decussation of various degrees (Fig. 6.43). All of these cases were male and the anterior corticospinal tracts were constantly larger than the contralateral lateral corticospinal tracts. In one case, the medullary pyramids showed hyperplasia; in the female cases, they were hypoplastic. These data are in line with other studies that abnormalities of the pyramidal tracts are often associated with X-linked conditions. Moreover, the high incidence of pyramidal tract abnormalities in trisomy 18 suggest a role of chromosome 18 in the normal development of the pyramidal tract, particularly of the pyramidal decussation. Recently, an uncrossed aberrant ipsilateral pyramidal tact was suggested for patients with congenital mirror movements caused by the *DCC* gene on chromosome 18 (Srour et al. 2010; Depienne et al. 2011).

This case was kindly provided by Hajime Miyata (Department of Neuropathology, Research Institute for Brain and Blood Vessels, Akita, Japan).

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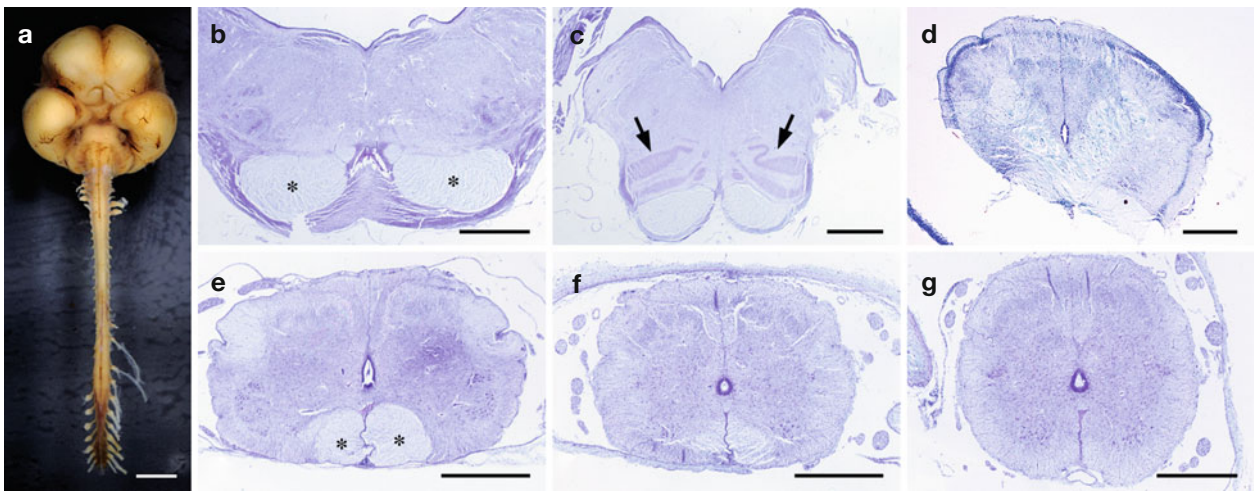

Fig. 6.43 Dominant uncrossed pyramidal tract in trisomy 18: (**a**) Formalin-fixed brain and spinal cord of a 21-gestational-week-old fetus with a male karyotype, showing hypoplasia of the pontine base and cerebellum; (**b**–**g**) transverse sections of the brain stem and spinal cord show relatively large pyramidal tracts without segmentation in the hypoplastic pons (*asterisks* in **b**), hook-shaped inferior olivary nuclei (*arrows* in **c**), the pyramidal decussation (**d**), and dominant anterior corticospinal tracts in the fourth cervical (*asterisks* in **e**) and sixth (**f**) thoracic segments. The corticospinal tract could not be clearly detected in the lower thoracic cord (**g**) (From Miyata et al. 2014; the photomicrographs were kindly provided by Hajime Miyata, Akita; with permission)

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