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REVIEW

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Development and malformations of the human pyramidal tract

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Abstract The corticospinal tract develops over a rather long period of time, during which malformations involving this main central motor pathway may occur. In rodents, the spinal outgrowth of the corticospinal tract occurs entirely postnatally, but in primates largely prenatally. In mice, an increasing number of genes have been found to play a role during the development of the pyramidal tract. In experimentally studied mammals, initially a much larger part of the cerebral cortex sends axons to the spinal cord, and the site of termination of corticospinal fibers in the spinal grey matter is much more extensive than in adult animals. Selective elimination of the transient corticospinal projections yields the mature projections functionally appropriate for the pyramidal tract. Direct corticomotoneuronal projections arise as the latest components of the corticospinal system. The subsequent myelination of the pyramidal tract is a slow process, taking place over a considerable period of time. Available data suggest that in man the pyramidal tract develops in a similar way. Several variations in the funicular trajectory of the human pyramidal tract have been described in otherwise normally developed cases, the most obvious being those with uncrossed pyramidal tracts.

A survey of the neuropathological and clinical literature, illustrated with autopsy cases, reveals that the pyramidal tract may be involved in a large number of developmental disorders. Most of these malformations form part of a broad spectrum, ranging from disorders of patterning, neurogenesis and neuronal migration of the cerebral cortex to hypoxic-ischemic injury of the white matter. In some cases, pyramidal tract malformations may be due to abnormal axon guidance mechanisms. The molecular nature of such disorders is only beginning to be revealed.

Key words pyramidal tract · corticospinal tract · development · developmental disorders · aplasia · hypoplasia · abnormal decussation

Introduction

The corticospinal tract invariably arises from layer-V pyramidal cells, particularly from rostral, frontal parts of the cerebral cortex. Both motor and somatosensory cortices give rise to corticospinal projections [4, 34, 61, 62, 80, 104]. Several motor areas on the medial surface of the macaque hemisphere give rise to corticospinal projections, including the supplementary motor area and various parts of the cingulate cortex [34, 35, 62]. With functional brain imaging comparable non-primary mo-

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tor areas have been found in the human cortex [42, 54, 110, 116] which, like the primary motor cortex, also have important roles in the control of hand and finger movements. Pyramidal tract damage can be assessed on magnetic resonance imaging (MRI) reconstructions [16, 36, 128, 130], with functional MRI [129] and transcranial magnetic stimulation [36, 129]. In man, the corticospinal or pyramidal tract is one of the latest developing descending pathways [3, 131]. Although the pyramidal tract already reaches the level of the pyramidal decussation at the end of the embryonic period, i. e. at eight weeks after fertilization, its further development is rather slow, and its myelination is not complete until the age of two to three years. Because of this slow development, malformations of the pyramidal tract may occur over almost the entire prenatal period.

In the present review, the development and malformations of the human pyramidal tract are described. Following a brief survey of the vast amount of literature on the development of the mammalian pyramidal tract, the development of the human pyramidal tract, its variations and malformations, the latter illustrated with autopsy cases, are discussed. In line with recent classifications of central nervous system malformations [12, 119], we use the following classification for malformations, in which the pyramidal tract may be involved: 1) malformations of induction; 2) malformations due to abnormal cell proliferation; 3) malformations due to abnormal neuronal migration; 4) malformations due to abnormal axon guidance mechanisms; and 5) malformations due to secondarily acquired injury, leading to destructive lesions. Moreover, certain malformations may lead to anomalies of pyramidal decussation.

Development of the pyramidal tract in rodents

The development of the pyramidal tract has been extensively studied particularly in rodents, much less so in primates. In rodents, in striking contrast to primates, the outgrowth of the corticospinal tract into the spinal cord occurs entirely postnatally [106, 126]. In rats, by embryonic day 14 (E14), the earliest corticofugal projections arise from preplate cells [30, 95], i. e. postmitotic neurons in the first cortical layer to develop. The preplate is later split into a marginal zone (layer I) and the subplate by cortical plate neurons that form layers II–VI. Most of the preplate cells later occupy the subplate. Axons of subplate cells may pioneer the pathway from the cerebral cortex into the diencephalon [30, 94]. Rat corticospinal neurons are generated on E15–E17 [93]. Cells of cortical layer V start growing their axons towards the internal capsule at least by the time (E16) when they arrive in the cortical plate [67]. Corticospinal axons traverse the diencephalon at E17.5, reach the cerebral peduncle at E19, the pontine nuclei at E19.5, and the caudal limit of the medulla oblongata at E20.5, just before birth [67, 121].

Early steps in the guidance of pyramidal tract axons

Corticospinal axon growth cones are set a formidable task in navigating through the internal capsule, cerebral peduncle, pons and medulla to reach their distant targets. This task is simplified by the fragmentation of their journey into shorter steps interrupted by intermediate targets or choice points, at which other cells provide critical *guidance cues* that direct growth cones on the next stage of their trajectory. The subpallium plays a prominent role in the guidance of corticofugal and thalamocortical axons [30, 95]. The early steps in the guidance of corticothalamic and pyramidal tract axons appear to be controlled by common mechanisms. Semaphorins regulate the initial extension of cortical axons towards the adjacent white matter through a complex mechanism involving repulsion from the outer, marginal zone and attraction from the inner, subventricular zone [9, 112]. Subsequently, corticofugal axons are attracted laterally towards the internal capsule by a mechanism that involves the chemoattractant netrin 1, which is prominently expressed in the ganglionic eminences [92, 113]. A critical decision point in the guidance of corticofugal fibers is located at the telencephalic/diencephalic boundary [87]. Corticofugal fibers enter the cerebral peduncle, and subsequently split into the layer-VI originating corticothalamic projections and the layer-V from which arises the pyramidal tract. Appropriate patterning of the basal telencephalon and hypothalamus is essential for guidance of corticospinal projections (Fig. 1). Loss of function of the homeobox gene *Nkx2.1* causes molecular transformation of the basal forebrain. In *Nkx2.1*-deficient mice, layer-V cortical projections take an abnormal path when coursing through the basal forebrain. Guidance of corticothalamic and thalamocortical axons is not impaired. The basal telencephalon and the hypothalamus repel the growth of cortical axons. The axon guidance molecule Slit2 may contribute to this activity. In *Slit2* mutant mice, corticofugal axons fail to enter the cerebral peduncle normally, and instead follow an abnormal course towards the surface of the telencephalon [10].

Spinal outgrowth of the pyramidal tract

Rat corticospinal fibers reach upper cervical segments shortly after birth, i. e. at postnatal day 0 (P0), the third thoracic segment at P3, the upper lumbar cord at P7, and the sacral spinal cord at P9 [57, 121]. After arrival of the first axons at a particular segment, new axons continue to be added to the tract for at least one week [57, 121,

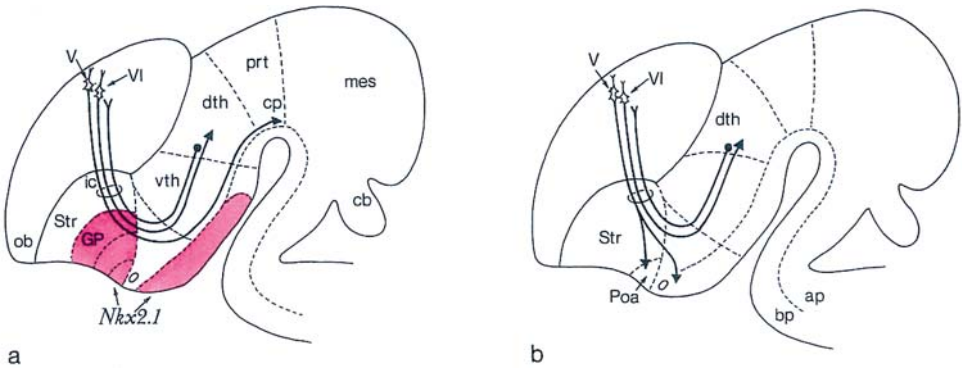

Fig. 1 The guidance of corticofugal projections at the telencephalic/diencephalic boundary [87]. The paths followed by corticospinal and corticothalamic axons are shown for wild-type (**a**) and *Nkx2.1* mutant mice (**b**). The grey areas in **a** show the normal expression pattern of *Nkx2.1* in the forebrain. *ap* alar plate; *bp* basal plate; *Cb* cerebellum; *cp* cerebral peduncle; *Ctx* cerebral cortex; *DT* dorsal thalamus; *GP* globus pallidus; *ic* internal capsule; *M* mesencephalon; *ob* olfactory bulb; *Poa* preoptic region; *PT* pretectum; *Str* striatum; *VT* ventral thalamus; *V, VI* cortical layers V and VI

122]. A delay of two days occurs between the arrival of corticospinal axons at a particular level of the spinal cord and their outgrowth into the spinal grey. Initially, most parts of the cerebral cortex including the occipital lobe innervate the spinal cord [69, 106, 127]. The withdrawal of collaterals correlates with the dramatic loss of fibers from the corticospinal tract during development [122]. O'Leary and co-workers [106] distinguished three stages in the development of cortical axons arising in layer-V neurons (Fig. 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. The homeodomain transcription factor *Otx1* plays an important role in this elimination process [143]. *Otx1* mutants are defective in the refinement of the exuberant, transient projections. In autosomal recessive mutant mice with extensive perturbations in the development of the cerebral cortex such as the reeler and yotari mice, corticospinal tract neurons are spread throughout all layers of the mutant cortex [65, 149]. The specificity of corticospinal connections is, however, relatively unaffected [135].

Several mechanisms control fiber outgrowth into the corticospinal target areas. A diffusible chemotropic signal may be 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 [63]. Similarly, the cervical spinal grey matter becomes innervated by corticospinal axons through the release of a diffusible chemotropic factor [71]. 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 [55]. The cell adhesion molecule L1 (L1CAM) may be involved in fascicle formation of outgrowing later arriving corticospinal fibers [51, 70]. In *L1* mutant mice, the *L1* mutation causes a primary pathfinding deficit in the development of the corticospinal decussation [21, 27]. A varying, but reduced number of corticospinal fibers was observed in the posterior columns of L1-deficient mice. These fibers did not extend beyond cervical levels. Moreover, a substantial number of corticospinal axons failed to cross the midline.

Mechanisms of pyramidal tract decussation

Various mechanisms are involved in the proper decussation of the pyramidal tract. During its outgrowth, Joosten and Gribnau [68] 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 fibers. 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 [19, 20]. Oligodendrocyte-associated neurite growth inhibitors (NI-35 and NI-250) in the already 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 [128]. Through Eph receptors, ephrin-B3 may function as a midline-anchored repellent that prevents corticospinal fibers from crossing back into the ipsilateral side of the spinal cord [78, 150]. Ephrin-B3, a ligand for the receptors EphB3 and EphA4, has a restricted expression pattern along the midline of the neural tube [14]. The receptor EphA4 is expressed in postnatal corticospinal neurons as their axons find their way down the contralateral spinal cord [33]. In ephrin-B3 mutant mice, corticospinal tract axons fail to respect the midline boundary of the spinal cord and bilaterally innervate both contralateral and ipsilateral motoneuron populations [150]. In EphA4-deficient mice, comparable observations were made [25]. Netrin-1 receptors also appear

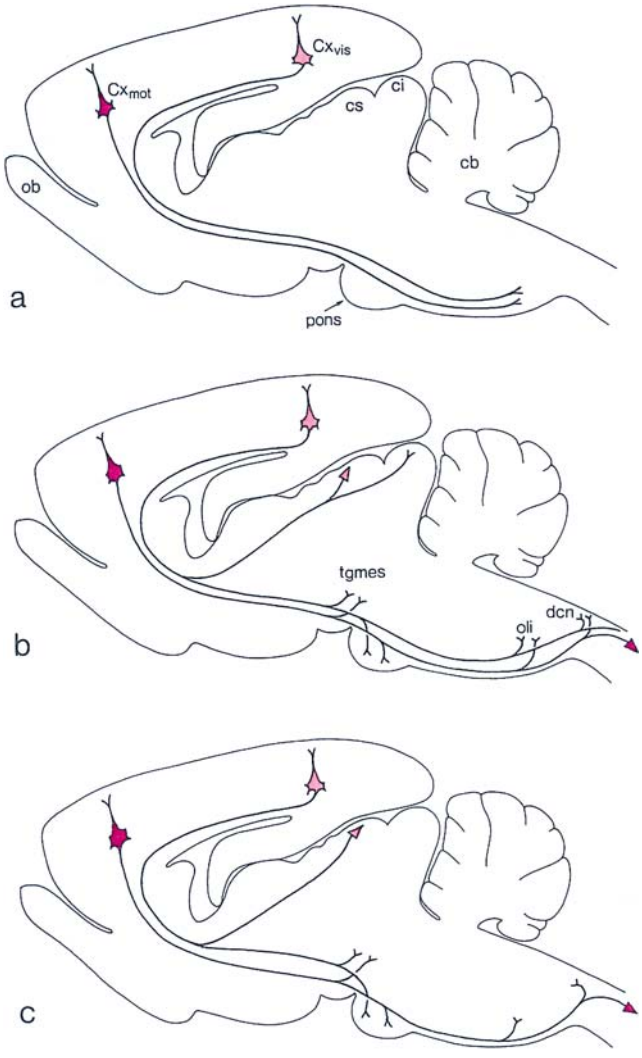

Fig. 2 Three stages in the development of cortical axons arising in layer-V neurons [106]. In **a** layer-V axons extend towards the spinal cord, bypassing their subcortical targets. In **b** the subcortical targets are exclusively contacted by collaterals that develop by branching off a spinally directed primary axon. In **c** 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. *cb* cerebellum; *ci* colliculus inferior; *cs* colliculus superior; Cx_{mot} motor cortex; Cx_{vis} visual cortex; *dcn* dorsal column nuclei; *ob* olfactory bulb; *oli* inferior olive; *tgmes* tegmentum mesencephali

to be necessary for a proper decussation of the pyramidal tract [41].

Development of the pyramidal tract in macaque monkeys

In rhesus monkeys, corticospinal fibers have reached at least the level of the lower cervical segments at birth [79]. Ipsilateral corticospinal projections are sparse in neonatal macaque monkeys [6, 53]. Tract-tracing experiments in fetal monkeys show that the areal distribution of corticospinal neurons in the cerebral cortex is larger than in infant macaques [53, 75]. Both the areal extent of the cortical origin and the relative number of corticospinal neurons with spinal axons regress very substantially over a period of two years [53]. The direct corticomotoneuronal projections do not appear to develop until six to eight months of age [79]. Lawrence and Hopkins [83] extensively studied the development of hand and finger movements in infant rhesus monkeys. The earliest signs of reaching were found at three to four weeks of age. Reaching was inaccurate and grasping of food was part of a rather gross whole arm and hand movement. Smooth reaching occurred in the third month and the first signs of relatively independent finger movements were present in the second and third month. Fully mature relatively independent finger movements were present at seven to eight months of age. This developmental time course correlates well with the appearance of corticomotoneuronal projections [6, 7, 29, 79]. The maturation of the monkey corticospinal tract was also studied using non-invasive transcranial magnetic stimulation of the motor cortex [43, 44, 107]. The latency of antidromic corticospinal volleys evoked from the pyramid and recorded from the motor cortex decreased dramatically during the first postnatal months. The fastest corticospinal fibers mature more rapidly over their cranial than their spinal course, where they undergo a tenfold change in conduction velocity from birth to adulthood. A correlation with the development of relatively independent finger movements was found.

Development of the human pyramidal tract

Since studies of the human corticospinal tract are necessarily non-invasive, they are substantially more limited than experimental studies in other primates. However, correlating carefully selected (mainly post-mortem) human studies of the pyramidal tracts with those in other primates has been fruitful. The development of the cerebral cortex may be divided into three, partly overlapping periods [88]: 1) an early, embryonic period characterized by the establishment of the preplate, which starts in about 40-day-old embryos; 2) an intermediate, fetal or migration period characterized by the formation of the cortical plate; the cortical plate is first visible at the end of the embryonic period (about 52-day-old embryos); and 3) a late, perinatal period characterized by specific phenotypic differentiation and functional maturation of cortical plate neurons, which starts about the 24th week of gestation. The separation between the fetal and perinatal periods is somewhat arbitrary but may be clinically relevant [88]. At that age prematures become viable. Moreover, in the fetal period

so defined, disorders of neuronal migration are likely to occur, and congenital or acquired abnormalities of the structural organization of the cerebral cortex are common in the perinatal period.

The first cortical layer to develop is the so-called *preplate* or *primordial plexiform layer*. During the formation of the cortical plate, the preplate is divided into the marginal zone (the future cortical layer I) above and the subplate below the cortical plate. The cortical plate gives rise to the cortical layers II–VI that are formed in an inside-out sequence, first layer VI, and subsequently layers V to II. Therefore, layer-V neurons are among the first cortical neurons that reach their place in the cortical plate. The first corticofugal projections originate in the first, embryonic period of cortical development [96]. Therefore, the corticospinal tract arises in a very immature cortical plate. Humphrey [64] studied the outgrowth of the human corticospinal tract with a silver technique (Figs. 3, 4). The corticospinal tract reaches the caudal medulla at stage 23 [64, 97]. After reaching the level of the pyramidal decussation at the end of the embryonic period, a rather long waiting period was found. Pyramidal decussation was complete by 17 weeks' menstrual or gestational age (15 postfertilization weeks), and a massive increase in the number of pyramidal tract fibers occurred at cervical levels between 16 and 17 gestational weeks. Lower levels of the spinal cord were reached by 19 (lower thoracic cord) and 29 (lumbosacral cord) gestational weeks (Fig. 4).

Using GAP43-immunohistochemistry, Eyre and coworkers [38] showed that by 29 gestational weeks, the corticospinal tracts are the only major tracts expressing this neuron-specific phosphoprotein in the lower cervical cord. 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-labeled axons may be derived from other spinal systems. At term, direct cortical projections to Ia-inhibitory interneurons were shown with electrophysiological techniques [38]. In man, the maturation of skilled finger movements requires a much longer period of development than in the rhesus monkey [46]. This maturation is also dependent on that of the corticospinal tracts [37, 98, 99]. During the first two years of life, a rapid decline was shown in the central conduction time of responses to magnetic stim-

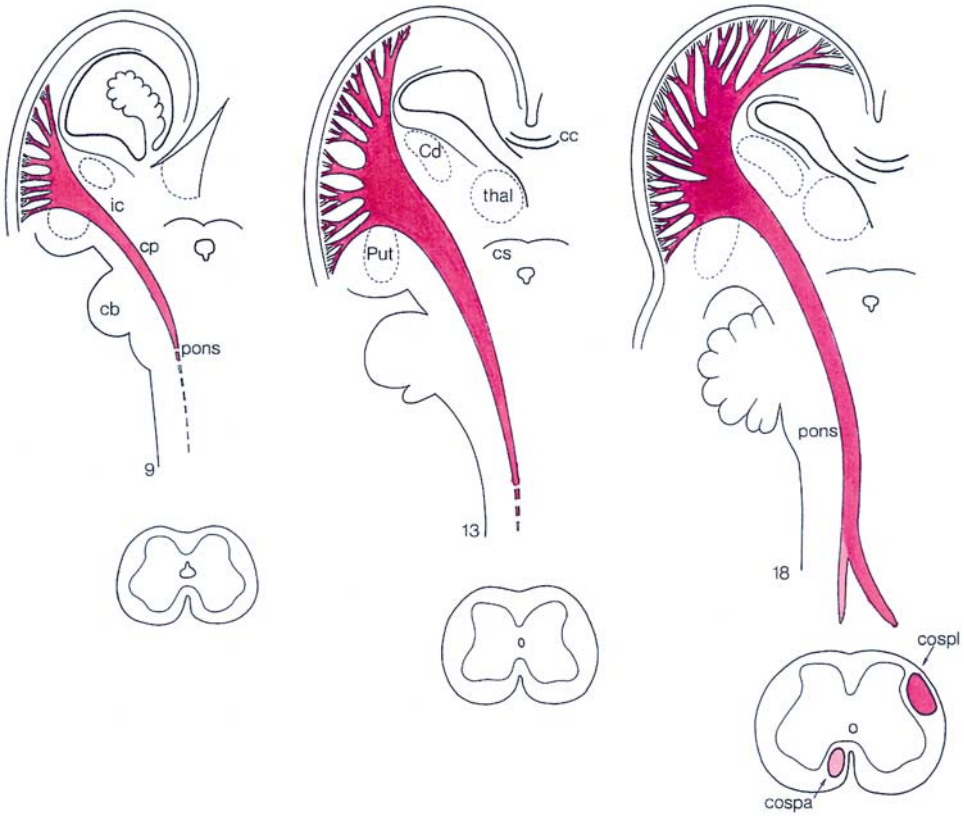

Fig. 3 The outgrowth of the human corticospinal tracts through the brain stem, shown for 9, 13, and 18 gestational weeks [3, 64]. *cb* cerebellum; *cc* corpus callosum; *Cd* caudate nucleus; *cospa, cospl* anterior and lateral corticospinal tracts; *cp* cerebral peduncle; *cs* colliculus superior; *ic* internal capsule; *Put* putamen; *thal* thalamus

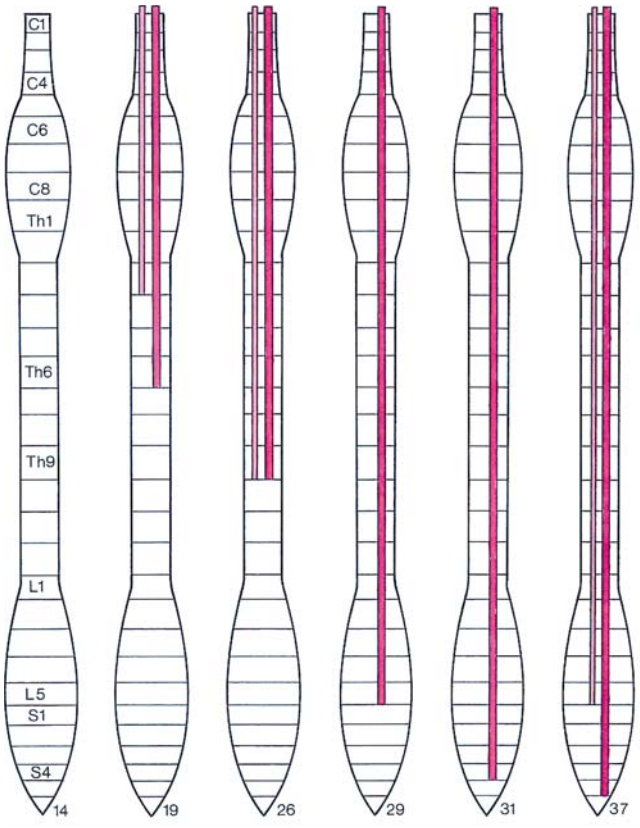

Fig. 4 The spinal outgrowth of the human corticospinal tracts, shown for 14, 19, 26, 29, 31, and 37 gestational weeks [3, 64]. The small bundles show the outgrowth of the anterior corticospinal tract (not identifiable in the fetal material of 29 and 31 weeks [3]), whereas the larger bundles show the outgrowth of the lateral corticospinal tract. C1,4,6,8, Th1,6,9, L1,5, and S1,4 indicate spinal segments

ulation of the cerebral cortex. Adult values for central conduction times were achieved around two to four 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 [38]. Neonates have ipsilateral corticospinal responses with shorter onsets than contralateral responses but similar thresholds and amplitudes [39]. Differential development was present from three 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 in at least two ways: 1) the prenatal establishment of some 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.

Myelination of the pyramidal tract usually starts at the end of the second or the beginning of the third trimester [17, 145, 147]. Wózniak and O'Rahilly [145] showed it to be already in progress at the level of the pyramidal decussation at 25 weeks of gestation. Myelination of the pyramidal tract occurs over a protracted period and is not complete until the age of two to three years [76, 147]. In the fetal and neonatal spinal cord (see Fig. 8a), the yet unmyelinated corticospinal tracts stand out as unstained areas in the white matter. The cranial part of the pyramidal tract is myelinated much earlier than its spinal part. The MRI pattern of myelination lags several weeks behind if compared with the histological timetable, probably due to the minimal concentration of myelin required on MR images [136].

Variations in the adult human pyramidal tracts

Nathan and co-workers [101] described the course, location and relations of the human corticospinal tracts within the spinal cord on the basis of autopsy material from patients with supraspinal lesions restricted to the corticospinal tracts or receiving anterolateral cordotomies. The lateral corticospinal tract is characterized by: 1) the large extent of the spinal white matter covered by the tract; 2) the separation in the lower cervical cord of fibers from the main mass of the tract, which reach the periphery of the cord in the anterolateral sector; and 3) its position dorsal to the dentate ligament in the cervical cord. The caudal extent of the anterior corticospinal tract depends on its size. When small it cannot be identified further caudally than the upper thoracic cord, but when large it continues into the sacral segments.

In 1876, Flechsig [45] already suggested that much of the pyramidal tract variability in man occurs at the pyramidal decussation. Several variations in the funicular trajectory of the human pyramidal tracts were described in otherwise normally developed cases [100, 101, 105, 148]. The pyramidal decussation may even be absent [100, 105, 138, 148] and aberrant pyramidal bundles may occur [80, 100]. Yakovlev and Rakic [148] studied the spinal cord of fetuses and neonates by staining for myelin sheaths. Since the pyramidal tracts were not yet myelinated, they could be followed as unstained bundles in their course through the medulla and the spinal cord. Partial decussation of the pyramidal tract was found in 66.9 % of the cases studied. Several variations were observed (see Fig. 5). In more than two-thirds of their specimens, the fibers of the left pyramid crossed to

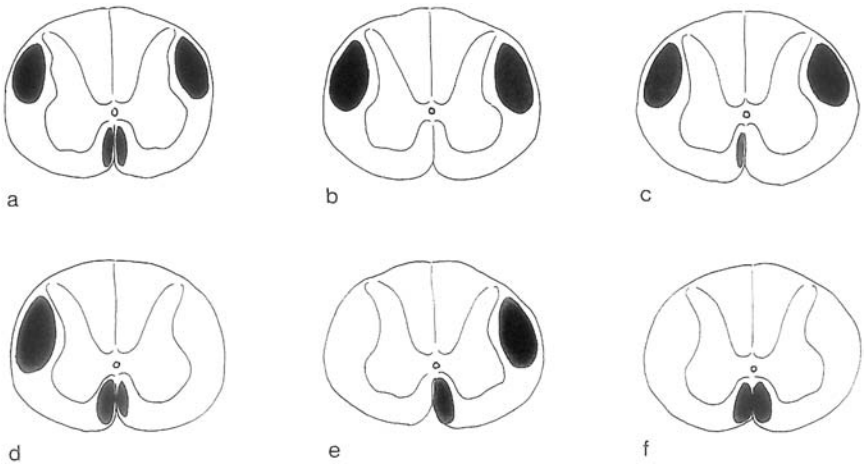

Fig. 5 The possible variations of the decussation of the pyramidal tracts [148]. In 66.9 % there was partial decussation of the pyramidal tracts, leading to a larger crossed and a smaller uncrossed pyramidal tract on both sides (**a**). Complete decussation of both pyramids with absence of both anterior pyramidal tracts was found in 16.2 % (**b**). In 13.9 % one pyramidal tract crossed completely (**c**). 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 (**d**) was not observed in Yakovlev and Rakic's series, but noted by others [103]. In one specimen the lateral and anterior pyramidal tracts were absent on the side of the completely crossed pyramid (**e**). In three specimens (2.3 %) complete absence of decussating bundles, leading to the absence of both lateral pyramidal tracts, was found (**f**)

the right side of the spinal cord at higher, more cranial levels in the decussation than the fibers of the right pyramid. Moreover, more fibers of the left pyramid decussated than of the right pyramid, whereas more fibers of the right pyramid than of the left one remained uncrossed. Therefore, the right side of the spinal cord, at least in the cervical region, receives more pyramidal tract fibers from both cerebral hemispheres than the left side. The resulting greater number of corticospinal fibers on the right side of the cord appears to be unrelated to handedness [74, 101].

Malformations of the human pyramidal tract

Malformations of the pyramidal tract may occur at various stages of development and, in general, are part of extensive malformations of the brain. They may be found in malformations due to induction defects, abnormal cell proliferation, abnormal neuronal migration, abnormal axon guidance mechanisms, secondarily acquired injury leading to destructive lesions, and in malformations leading to anomalies of decussation. In Figs. 6–8 some examples of aplasia and other malformations of the pyramidal tract are shown. Aplasia of the

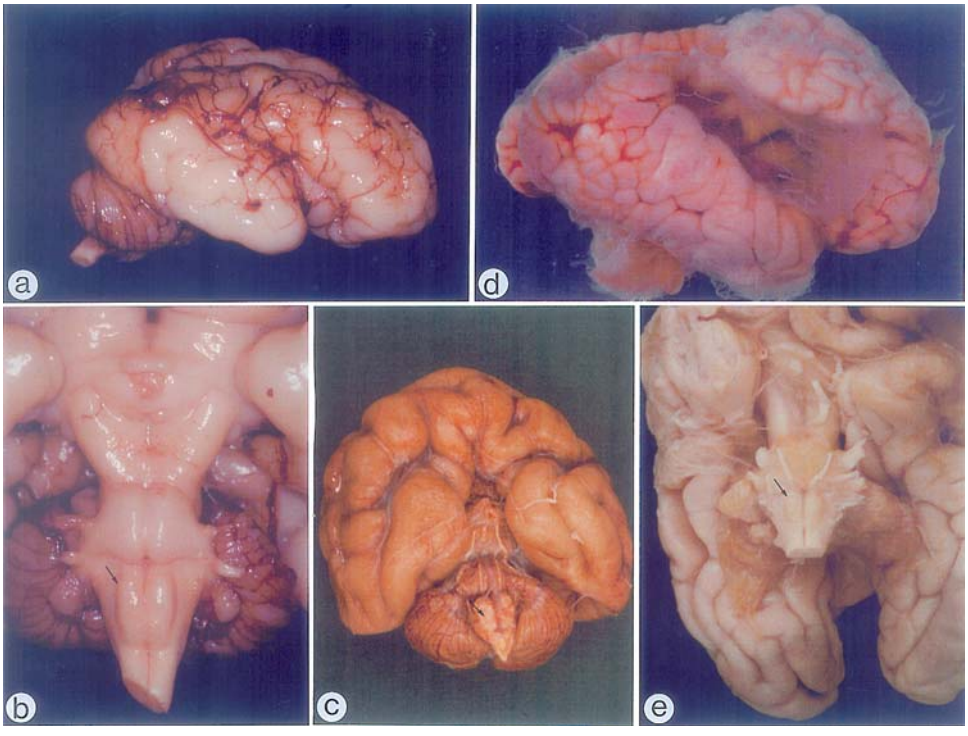

Fig. 6 Macroscopy of some examples of developmental disorders of the pyramidal tracts: **a, b** lateral and basal views of the brain in an extreme, familial case of microcephaly [132, with permission from Springer]; **c** basal view of the brain of a holoprosencephaly case; **d, e** lateral and basal views of a case of porencephaly. Note the medially located inferior olives in all cases (small arrows)

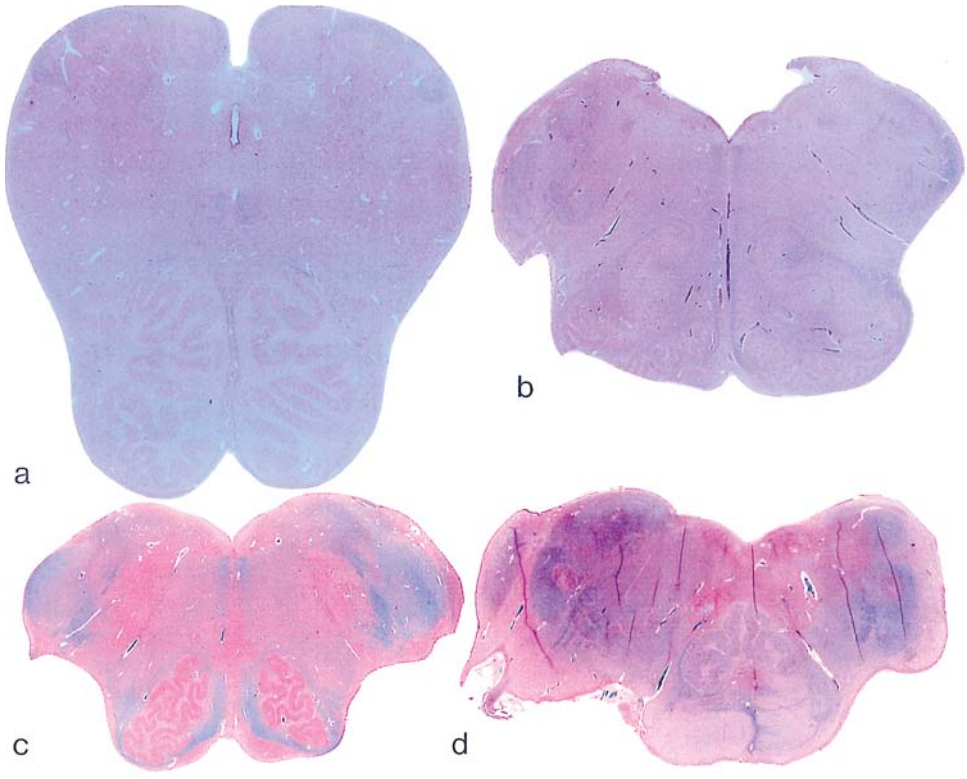

Fig. 7 Microscopy of the pyramidal tracts at the medullary level. Absence of the pyramids is shown for: **a** an extreme, familial case of microcephaly [132, with permission from Springer]; **b** holoprosencephaly, and **c** X-linked hydrocephalus. In **d** brainstem malformations including medial inferior olives above malformed pyramids, possibly leading to non-decussation of the pyramidal tracts (see Fig. 8 f) are shown for a severe, lethal form of the Möbius syndrome

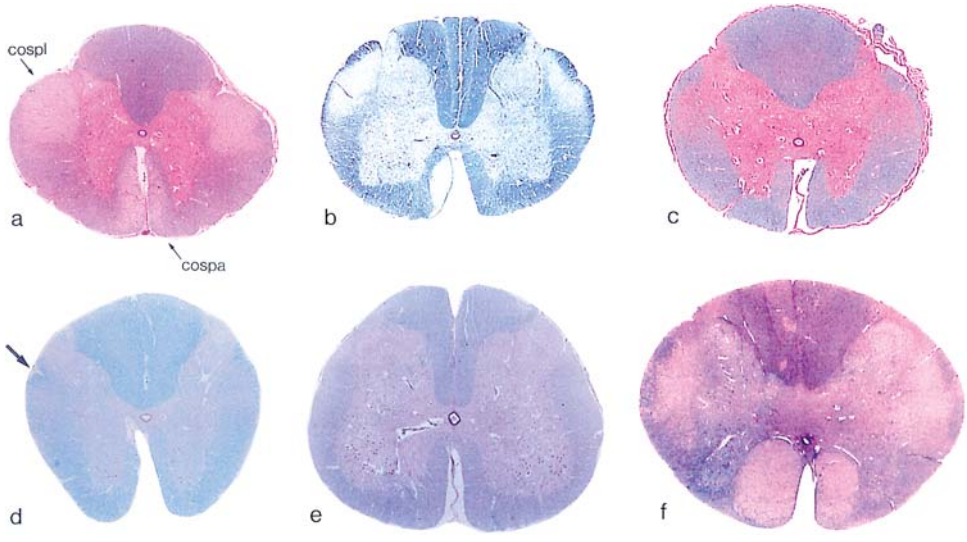

Fig. 8 Microscopy of the pyramidal tracts at the spinal level. In a neonatal control case (**a**), the corticospinal tracts stand out in the thoracic cord as unstained pathways. Complete crossing of one pyramidal tract is shown in another neonatal control case (**b**). Absence of the corticospinal tracts is shown for: **c** X-linked hydrocephalus (thoracic cord); **d** a microcephaly case (thoracic cord); note the abnormal sulcus just below the dorsal horn (arrow); and **e** holoprosencephaly (lumbar cord). In **f**, non-decussation of the pyramidal tracts is shown for a severe, lethal form of the Möbius syndrome (cervical cord). *cospa* anterior corticospinal tract; *cospl* lateral corticospinal tract

corticospinal tracts causes marked reduction of the size of the cerebral peduncles and crowding of the pontine nuclei. The medulla has no pyramids, and the inferior olivary nuclei abut the ventral surface of the medulla, covered by a thin layer of marginal glia. In the spinal cord, the normal-sized posterior funiculi predominate, and the dorsal horns are rotated laterally. The lateral and anterior funiculi are very small. An abnormal sulcus may be seen at the lateral surface of the cord (Fig. 8c). After damage occurring during the fifth and sixth fetal month, the pyramids are hypoplastic and the spinal cord may show relatively small, hypoplastic tracts. Lesions at a later stage of development induce corticospinal tract degeneration rather than aplasia. The degenerated corticospinal tracts stand out as pale, non-myelinated zones [48].

Pyramidal tract malformations due to induction defects

The embryonic period in man can roughly be subdivided into the following phases: 1) formation and separation of the germ layers; 2) dorsal induction, and 3) ventral induction. During the separation of the germ layers enterogenous or neurenteric cysts, extending into the vertebral canal, may arise as well as the so-called split notochord syndrome. These malformations may severely compress the spinal cord [109, 134]. During the dorsal induction phase the neural tube defects arise. Aplasia of the corticospinal tracts is a consistent feature in anencephaly [84]. It has also been noted in occipital encephaloceles [73]. In syndromes with encephaloceles such as the Meckel-Gruber syndrome, a triad of prosencephalic dysgenesis, occipital encephalocele and rhombic roof dysgenesis, the pyramids are also absent [1, 22]. In myelomeningoceles, the consequences of the spinal lesion depend on the level, which in 80 % of cases is located at the lumbosacral level. With lesions above L3, there is complete paraplegia. The characteristic developmental malformation of the ventral induction phase is holoprosencephaly. In its most severe, alobar form the corticospinal tracts are usually missing [48, 103], whereas in the less severe, semilobar and lobar forms of holoprosencephaly the pyramidal tracts are either absent or hypoplastic (Figs. 6c, 7b, 8e). In Apert's syndrome, the most common form of craniosynostosis due to a disturbance in the formation of the skull base in the ventral induction period, hypoplastic pyramids were found [24, 86].

Pyramidal tract malformations due to abnormal cell proliferation

Aplasia of the corticospinal tracts is also found in cases of severe microcephaly [23, 103, 108, 132, see Fig. 6a, b], in microlissencephaly [13], and in certain chromosomal disorders. Uncommonly large pyramids were found in three cases of cerebellar hypoplasia [4]. Bilateral corticospinal tract hypertrophy was found in the X-linked form of Kallmann syndrome [77]. Unilateral hypertrophy of the pyramidal tract is uncommon, and usually is associated with an early destructive lesion in the contralateral hemisphere [48, 137]. It may also occur in hemimegalencephaly with its obvious asymmetry of the pyramids [28, 114].

Pyramidal tract malformations due to abnormal neuronal migration

Disorders of neuronal migration of the cerebral cortex are currently divided [12] into: 1) the lissencephaly/subcortical band spectrum; 2) the cobblestone complex (Walker-Warburg and related syndromes); 3) heterotopia; 4) polymicrogyria and schizencephaly, and 5) malformations of cortical development, not otherwise classified (e. g., Zellweger syndrome). Aplasia or hypoplasia of the pyramidal tract may occur in neuronal migration disorders of the cerebral cortex, especially in the Walker-Warburg syndrome with its severe white matter changes [48, 60, 103, 144]. In the related Fukuyama type of congenital muscular dystrophy and muscle-eye-brain disease, the pyramidal tracts are hypoplastic [52, 118]. In classic or type 1 lissencephaly, the pyramids are hypoplastic or absent [48, 103, 115]. In subcortical band heterotopia (SBH) or 'double cortex', bilateral, extensive plates of heterotopic grey matter are found beneath the cortex. With functional MRI it was shown that, despite its epileptogenic activity, SBH seems to be responsible for part of the functional activity [111]. This suggests that the double cortex in SBH participates in the formation of the corticospinal tract. In an animal model for SBH, the *'tish'* rat, the double cortex has reciprocal connections with the thalamus and the other hemisphere, and, moreover, gives rise to part of the contralateral corticospinal projection [120]. In polymicrogyria and schizencephaly, hypoplastic to absent pyramidal tracts may occur [18, 58, 81]. It has also been described in a familial form of schizencephaly due to an *EMX2* mutation [56]. In Zellweger syndrome, a mitochondrial disorder, the pyramidal tracts are hypoplastic or absent [142].

Pyramidal tract malformations due to abnormal guidance mechanisms

Although in mice an increasing number of genes has been found to play a role during the development of the pyramidal tract, and mutants show pyramidal tract malformations, such malformations in man are so far restricted to *L1CAM* mutations. Sarnat [119], however, suggested that, in the light of animal data, netrin downregulation may occur. Loss of *NKX2.1* and *SLIT2* expression may also be found in the near future. Chow and colleagues [22, 59] 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 (see Fig. 7c). X-linked hydrocephalus was first described in a British family with several male sibs that died at birth from congenital hydrocephalus due to aqueduct stenosis [15]. The discovery that *L1CAM* mutations may lead to an X-linked recessive disorder with manifestations including hydrocephalus, adducted thumbs, spastic hemiplegia due to hypoplasia of the corticospinal tracts, hypoplasia or agenesis of the corpus callosum and mental retardation, led to a steadily in-

creasing list of familiar and isolated cases. Since the first mutation report [117], more than 100 families and isolated cases with *L1CAM* mutations have been described [40, 47]. 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 paraplegia type 1 represent phenotypic variants of *L1CAM* mutations. In a screening study of 153 cases with prenatally or clinically suspected X-chromosomal hydrocephalus [40], a mutation detection rate of 74.2 % was found 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 contrast to data in mouse mutants, in a 2-week-old male with an *L1CAM* mutation, normal pyramidal decussation and axonal projections to the spinal cord were found [32].

Malformations of the pyramidal tract due to secondarily acquired injury

Absence of the corticospinal tracts may also occur in many cases of antenatal and perinatal encephaloclastic, destructive lesions such as porencephaly (Fig. 6d, e) and hydranencephaly [50, 103, 125]. In porencephaly a communicating "hole"-like lesion is found, whereas in hydranencephaly complete destruction of the cerebral hemispheres has resulted. Porencephaly and hydranencephaly are residual to the destruction of brain tissue from a failure in carotid circulation or fetal infection, especially toxoplasmosis and cytomegalovirus, and differ only in terms of the extent of the damage [48, 50, 60, 103, 125, 140]. Affected infants show severe mental retardation and spastic quadriplegia. Absence of one pyramid was also noted in a case of traumatic amniocentesis [124].

The most common type of pyramidal tract damage is due to hypoxic-ischemic injury of the cerebral white matter [11, 125, 140]. It has an increasing prevalence as smaller, more premature infants survive because of better neonatal care. In younger premature infants (22- to 30-week-old), the blood vessels of the germinal, periventricular zone and the perforating vessels of the external glial limiting membrane are particularly vulnerable to perinatal asphyxia [89]. Damage to these vessels often causes focal hemorrhagic lesions. In older premature infants (30–34 weeks), the fetal periventricular white matter seems to be particularly vulnerable to hypoxic-ischemic injury, leading to periventricular leukomalacia (PVL), and often resulting in infarction (necrosis) and cavitation [90, 91]. PVL refers to necrosis of white matter in a characteristic distribution, i. e. in the white matter dorsal and lateral to the external angles of the lateral ventricles. The corticospinal tracts run through the periventricular region. Therefore, impaired motor function is the most common neurological sequel of periventricular white matter injury [2, 11, 31, 128, 130]. MRI studies [16, 36, 128, 129] show that the amount of Wallerian degeneration visible by asymmetry of the brain stem in hemiparetic children correlates well with motor dysfunction. Pyramidal tract damage correlates with motor dysfunction in PVL [130]. Epidemiological and experimental studies have demonstrated a strong association between materno-fetal infections and the development of PVL and cerebral palsy [72, 102, 140, 141]. Another major pathogenetic factor is the maturation-dependent vulnerability of oligodendrocyte progenitors [8].

Malformations leading to anomalies of pyramidal tract decussation

Anomalies of the decussation of the pyramidal tract are mostly nonspecific, coincidental anomalies [85, 103, 115, 139], but are frequently found in posterior fossa malformations such as occipital encephaloceles [138], the Dandy-Walker malformation [26, 66, 82], Joubert syndrome [49, 133, 146], and in cases with extensive malformations of the brain stem such as Möbius syndrome (see Fig. 8f).

Conclusions

This survey of the neuropathological and clinical literature reveals that malformations of the pyramidal tracts may occur in a large number of developmental disorders. Most of these disorders form part of a broad spectrum, ranging from disorders of patterning, neurogenesis and neuronal migration of the cerebral cortex to hypoxic-ischemic injury of the white matter. Given the formidable task of corticospinal tract axons to find their way through the internal capsule, brain stem and spinal cord, and the number of genes involved, it is surprising that so few defects have been found so far in axon guidance mechanisms of the human pyramidal tract. The molecular nature of such disorders is, however, only beginning to be revealed.

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