The Challenge of Axonal Path-Finding

ABSTRACT Congenital syndromes of altered nervous system connectivity are reviewed along with recent findings on axonal growth: achiasma, congenital nystagmus, congenital horizontal gaze palsy, mirror movements and the syndromes of Kallmann, Wildervanck, Duane and Marcus Gunn. Identical guidance molecules are most likely involved in making axonal connections after injury and during development. Thus, investigations into variants of connectivity may help develop strategies to treat disconnections of axons in the adult.

KEYWORDS Axonal growth cone; congenital nystagmus; guidance molecules; mirror movements

INTRODUCTION

Muscle twitches around the mouth whenever the eye blinks are frequently seen after recovery from facial palsy and are attributed to misrouting of motor axons. If secretory axons re-grow imperfectly, “crocodile tears” result as abnormal responses to gustatory stimuli. Incredibly more complex processes occur during development, if we consider that roughly $10^{10}$ neurons in the human central nervous system (CNS) demand proper connections. The present paper reviews observations related to abnormal wiring within the visual and ocular motor pathways and claims that the challenge of axonal path-finding has yet to be faced by clinicians.

THE AXONAL GROWTH CONE

Central to the establishment of CNS connectivity is the highly sensitive tip of the growing axon, a fan-shaped motile structure with finger-like extensions. En route to its target region, the growth cone has to take the proper turns and, at its final destination, must cease extending to form synapses in an orderly, e.g. retinotopic, manner. Astonishing videos of this target-searching behavior are available (Oster & Sretavan, 2003).

Axon-guiding molecules, mainly identified in worms, flies and mice, form highly conserved families of proteins and corresponding receptors. Synergy of a relatively small number of factors appears sufficient to generate the intricate wiring of a mature CNS (Dickson, 2002). A well-studied model is the developing retinal ganglion cell (Oster & Sretavan, 2003): Involved in visual system maturation are the fasciculation of axons on their way to the optic nerve, the selective midline crossing at the optic chiasm and the mapping of neighboring retinal
cells onto neighboring target sites. Ephrin guidance molecules are expressed in a graded manner in the target region and corresponding Eph receptors on ganglion cells again show a concentration gradient. Graded expression of attractants and repellents appears central to the generation of topographic maps.

**INSTANCES OF FAILED AXONAL PATH-FINDING**

**Achiasma and Congenital Nystagmus**

The “achiasma syndrome” has been identified in three females with a see-saw pattern congenital nystagmus (Apkarian & Bour, 2001). Absence of optic nerve decussations was documented by abnormal evoked potentials and neuroimaging. Animal experimentation suggests the involvement of multiple factors, such as Pax-2, EphB, Slit 1 and Slit 2, in midline crossing of retinal ganglion cell axons and thus chiasma formation (Thanos et al., 2004).

Most forms of congenital nystagmus are probably due to wiring defects in the visual or ocular motor pathways. In contrast to the achiasma syndrome without contralateral projections, these are abnormally increased in albinism (Hoffmann et al., 2003).

**Congenital Horizontal Gaze Palsy**

Absent horizontal eye movements have recently been traced to mutations in the ROBO3 axonal guidance gene (Jen et al., 2004). The resulting syndrome of HGPPS (familial horizontal gaze palsy with progressive scoliosis) shows hindbrain dysplasia with probable absence of the abducens nuclei and electrophysiological abnormalities (Jen et al., 2004): its absent decussations in the somatosensory and corticospinal tracts are reminiscent of the “non-decussating retinal-fugal fiber” or achiasma syndrome.

**Mirror Movements**

Another variant of motor organization underlies mirror movements (MM), involuntary contralateral movements whenever willed limb movements are performed on one side (Fig. 1a). MM occur in Kallmann syndrome, as an autosomal dominant trait without associated abnormalities or in association with vertebral fusion (Danek, 1998; Danek et al., 1992; Royal et al., 2002; Wildervanck, 1978).

Motor evoked potentials disclose a specific corticospinal abnormality: whereas FHGPS patients show only ipsilateral and normal subjects strictly contralateral responses (Fig. 1b), in MM they are distributed bilaterally (Fig. 1c). Manipulation of ephrin/Eph signalling has reproduced the MM phenotype in mice. Without EphA4 receptors or ephrin-B3 they simultaneously move right and left limbs and their corticospinal projections re-cross in spinal gray matter. Thus, one motor cortex connects with both body halves. Binding of growth cone EphA4 to midline ephrin-B3 provides the repulsive signal that prevents the projections from re-crossing (Kullander et al., 2001a and b).

**Hypogonadotropic Hypogonadism with Hyposmia (Kallmann Syndrome)**

Kallmann syndrome (KS) was the first clinical syndrome with a proven disorder of axonal path-finding. Mirror movements are associated only with X-linked KS (Danek, 1998; Danek et al., 1992). The product of the responsible gene, anosmin-1, is involved in making connections between the olfactory bulb and axons of the olfactory placode entering the skull at the cribriform plate (Hu et al., 2003). Cells containing gonadotropin move along this pathway into the hypothalamus. Thus, the perplexing combination of hypogonadotropic state with impaired sense of smell was finally understood.

**Cervico-Oculo-Acuticus Syndrome (Wildervanck Syndrome)**

This complex syndrome is highly suggestive of abnormalities of axonal path-finding and combines Duane’s anomaly with malformation of the cervical cord and of the ears (Wildervanck, 1978). A personal case with extensive cervical fusion (Fig. 2) also displayed MM (Danek, 1998; Danek et al., 1998). Similar to earlier cases, there was association with crocodile tears (Biedner et al., 1979; Karsenti et al., 1984). Possible gene candidates are the so-called homeobox genes also involved in segmentation of the vertebral column.

**Duane’s Anomaly**

This syndrome of deficient horizontal eye movements (Alexandrakis & Saunders, 2001) is suggestive of axonal malrouting with innervation of the lateral rectus muscle by the oculomotor nerve because of sixth nerve absence ( Parsa et al., 1998). To explore the range of possible associated abnormalities, we clinically examined 10 cases with either bilateral or familial
FIGURE 1 (a) Congenital mirror movements, schematic representation: Whenever the right hand moves (continuous arrow) there is associated unwanted symmetric activity in the left hand (broken arrow) and vice versa (modified after Royal et al., 2002). (b) Typical result of focal transcranial magnetic stimulation of the motor cortex hand area in a control subject: responses restricted to the contralateral hand. (c) Result in patient with Wildervanck’s syndrome and mirror movements: bilateral responses indicate variant corticospinal tract organization.

unilateral Duane’s anomaly. Interestingly, only one subject displayed extraocular findings (unilateral mandibular hypoplasia and anakusis) and none had MM or spinal symptoms (Danek, 1998; Danek et al., 1998). Still, combinations of Duane’s anomaly with the Kallmann or Wildervanck syndrome (Cordonnier et al., 1992; Wildervanck, 1978) and other patterns (Isenberg & Blechman, 1983; Kohlhase et al., 2002) speak to the enormous number of guidance processes that can be disturbed.

**Congenital Cranial Dysinnervation Disorders**

Subsequently, the whole group of cranial innervation variants was grouped under the heading of CCDD (congenital cranial dysinnervation disorders), with Duane’s syndrome and HGPPS figuring prominently in the subgroup with predominant horizontal disorders of ocular motility (Gutowski et al., 2003). Syndromes of congenital fibrosis of extraocular muscles (CFEOM) and of congenital ptosis share vertical motility impairment. In particular, synkinesis of the superior rectus muscle and the levator palpebrae superioris was recently recognized as a cause of failure in surgery for congenital ptosis (Brodsy, 2000; Harrad & Shuttleworth, 2000). Congenital facial palsy syndromes, including Möbius syndrome with both facial and ocular movements affected, are recognized as the third group among the CCDDs for which an ever increasing number of gene loci are being found (Gutowski et al., 2003).

**Marcus Gunn’s Phenomenon**

In this final example, also known as “winking jaw,” jaw movements cause elevation of an often ptotic eyelid
Abnormal segmentation of the vertebral column may be associated with disorders of axonal guidance: X-ray from the patient with Wildervanck’s cervivo-oculo-acusticus syndrome shows cervical fusions, the Klippel-Feil anomaly, to an extent that a stick-like bony neck resulted (courtesy of Neuroradiology, Munich University).

(Fig. 3). Again, there are peculiar combinations with other instances of suspected axonal malrouting (Kodsi, 2000). In the inverse phenomenon of Marin Amat, the eye narrows with jaw movements. Both types of “palpe-bromandibular synergy” also develop after facial nerve injury (Jogiya & Sandy, 2003) and together with congenital as well as acquired forms of “crocodile tears” close a circle (Biedner et al., 1979; Karsenti et al., 1984). They connect deficient axonal path-finding in the developing nervous system with instances where injured axons cannot re-establish their connections but follow alternative pathways.

**CONNECTING THE PRESENT WITH THE FUTURE**

Is there any advantage if clinicians know about the syndromes listed above or are these mere footnotes to basic science chapters on CNS connectivity?

For an individual with variant axonal pathways, there is no obvious benefit if the molecular mechanism is identified: the connections are in place and unlikely to change. Identification of responsible genes, however, does allow much better family counseling. Knowledge of the whole spectrum of a disorder will be beneficial for prognostic evaluation and can improve the treatment of complications, such as of scoliosis in FHGPS or hypogonadism in Kallmann syndrome.

On a more general level, identical guiding molecules are probably involved in development and in adult axon regeneration. As for the spinal cord (Schwab, 2002), new therapies could also become available for the visual system.

Last but not least, many of us take pleasure in more erudite diagnoses and in connecting clinical observation with basic science insights. A particular challenge here is posed by synesthetic phenomena, the merging of sensory information that undoubtedly has a genetic background (Baron-Cohen et al., 1996). Color-grapheme synesthesia, where specific color sensations are associated with specific letters or digits, is perhaps based on connections that are only present in the brains of a select few.

In any case, we should look for additional clinical signs of abnormal connectivity: after all, axonal misrouting must be common given the many possibilities for mishap among the myriad connections needed to build a mature CNS! Thus, in patients with congenital nystagmus, Marcus Gunn’s or Duane’s phenomena, some time should be spent inspecting the optic nerve head, asking about the sense of smell, having the patient move his neck or recording evoked potentials to check for abnormal projection patterns of albinism or...
achiasma. The easiest of these maneuvers is having the patient move the fingers of each hand separately and watching for mirror movements (Fig. 1a), a clear indication of variant connectivity.

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REFERENCES


