Aberrant peripheral nerve fibres in the medulla oblongata of man

WILLIAM DEMYER¹

From Indiana University School of Medicine, Indianapolis, Indiana, U.S.A.

Occasionally peripheral axons with Schwann cell sheaths penetrate the neuraxis. In many instances, the fibres are misdirected nerve rootlets regenerating in proximity to an intra-axial lesion such as traumatic cysts, inflammation, or neoplasm (Klintworth, 1964; Druckman and Mair, 1953; Hughes and Brownell, 1963). In other instances (Staemmler, 1939; Riggs and Clary, 1957), as in the present example of aberrant fibres within the medulla oblongata, no local intra-axial lesion was apparent.

MATERIAL AND METHODS

The patient, an 82-year-old white man, died with emphysema and renal failure. He had been blind for several years because of cataracts. On admission, he was semistuporous. His chart recorded no other neurological deficits, either by history or physical examination, but he had not been interrogated or examined by a neurologist. He had no signs of neurofibromatosis clinically or on necropsy. The cerebral vessels were sclerotic. The left occipital lobe was infarcted, and the brain-stem, basal ganglia, and the right cerebellar hemisphere showed a few small, scattered ischaemic areas. Grossly the medulla oblongata was normal.

The patient was one of 14 consecutively necropsied, from whom medullae were selected for the purpose of studying the junction zone of the area postrema with the funiculus separans (DeMyer, 1965, in preparation). After fixation by immersion in 4% formaldehyde, the medullae were embedded in paraffin. Serially cut at 16 μ , the sections were alternately stained by Nissl and Spielmeier methods, and silver impregnated after Hortega for neurites, as adopted for paraffin sections (DeMyer, 1958). The sections were continued caudally through the obex to the level of the central canal of the spinal cord.

OBSERVATIONS

Of the 14 serially sectioned medullae oblongata, only the 82-year-old man's had peripheral nerve fibres within the neuraxis. Aberrant fibres first appeared in the caudal rootlets of the vagus nerve

and were distributed bilaterally, as shown in Figure 1. Some penetrated the lateral aspect of the medulla along the usual course of the vagal rootlets, as shown at point 1 in Figure 1. Others could be traced dorsally outside of the pia mater, around the circumference of the medulla. Some fibre bundles entered the neuraxis in company with blood vessels, particularly with the long circumferential vessels penetrating dorsolateral to the nucleus solitarius (point 2 of Figure 1). The most dorsal site of penetration was just lateral to the lingula (point 3 of Figure 1). At point 3, the bundles of axons directly penetrated the pia mater and mingled with the subpial glia. Once inside the neuraxis, the fibres passed through the area postrema, extending along vessels as far ventral as the hypoglossal nucleus. From the sites of pial perforation, the number of axons dwindled in proportion to their distance from the surface. Identification of the aberrant fibres, whether intra-axial or extra-axial, was easy because the axons had a very tangled, interlacing course as shown in Figure 2.

Typical Schwann cells accompanied the axons intra- and extra-axially. The calibre of the axons

FIG. 1. The dark lines encircling the dorsal aspect of the medulla oblongata illustrate the bilateral course of the aberrant peripheral nerve fibres. The numbers show the sites of penetration of the neuraxis.

¹Special fellow, National Institute of Neurological Diseases and Blindness, United States Public Health Service (NB 18404)

FIG. 2. Silver carbonate impregnation which shows peripheral nerve fibres coursing through the area postrema. The ventricular surface of the area postrema is on the upper left. At the upper right, the nerve fibre bundles are seen around large vessels. In the middle of the field, the large fibre bundle is accompanied only by a capillary. Notice the characteristic whorled, interlacing course of the axons.

varied from small to large. Many of them were in the 10-15 μ range. In the Spielmeyer stain, only a few of the intra-axial peripheral nerve fibres had myelin sheaths, but when extra-axial, the fibres were well myelinated.

Collagen fibres, corresponding to endo- and perineurium, could be found between and around the axons throughout their course. Collagen fibres were identified by their typical appearance in silver-impregnated sections. When recently-fixed material is impregnated with silver carbonate, axons are deep purple to black, while collagen is a bright pink. Tinctorial as well as morphological features permit a fairly reliable distinction to be made.

Although the medulla of this patient showed scattered axonal degeneration and other changes

compatible with senility, neither the parenchyma of the medulla nor the meninges showed any lesions, such as inflammation or infarction, which might have predisposed to the ingrowth of axons. However, the vessels were sclerotic, and the right cerebellar hemisphere had small ischaemic areas.

DISCUSSION

Any doubt that the structures identified as nerves contain axons is dispelled immediately by the completely characteristic appearance of the axons in the silver carbonate impregnation and by their continuity with rootlets of the vagus nerve. The point of major interest is the pathogenesis of the aberrant fibres. Most likely, they arose from dorsal root ganglia or ventral root fibres of the vagus nerve. The well-reasoned arguments of previous authors against interpreting intra-axial peripheral nerve bundles as normal perivascular fibres need not be repeated here. However, the bundles may represent hypertrophic perivascular fibres (Klintworth, 1964; Riggs and Clary, 1957; Lu, Kypridakis, Abbott, and Vogel, 1963; Pitts and Riggs, 1964). Most authors draw an analogy between the tangled course of intra-axial peripheral fibres with amputation neuromas in transected nerves (Klintworth, 1964; Druckman and Mair, 1953, Hughes and Brownell, 1963). The implication is that the cause of the aberrant fibres in the present case would be a transecting lesion followed by regeneration. For many previous cases, the postulated mechanism of transection-regeneration seems amply supported by the presence of an obvious predisposing lesion. In the present case, no lesion was apparent (or scarcely can be imagined) which could account either for the symmetrical disposition of the aberrant fibres or their penetration of an apparently normal pia mater and neuraxis. Inasmuch as previous authors (Riggs and Clary, 1957; Lu *et al.*, 1963; Pitts and Riggs, 1964) indicate that the incidence or at least the prominence of intra-axial peripheral nerve fibres increases with age, one must admit the possibility that the fibres developed by transection-regeneration or some hypertrophic mechanism in later life. The one plausible transecting agent apparent in the current case would be ischaemic damage to the vagus rootlets from vascular disease, which was prominent.

Experimental studies (Jakoby, Turbes, and Freeman, 1960; Turbes and Freeman, 1958) as well as observations on human material (Freeman, 1961) indicate that regenerating nerve fibres, even after dorsal rhizotomy (Hughes and Brownell, 1963), usually fail to penetrate normal meninges, normal neuraxial substance, or glial scars, although invasion can be promoted pharmacologically (Windle,

Clemente, and Chambers, 1952). Apparently an important condition for ingrowth of peripheral axons in postnatal animals is that normal barriers be destroyed or bypassed. Since the fibres in the present case were bilateral, penetrated normal neuraxis and meninges, and intermingled with glia at their penetration points, the question arises whether they grew in during embryogenesis. If so, the one normal element missing at the neuraxial junction was the Obersteiner-Redlich zone. The free ingrowth of Schwann cells with aberrant fibres suggests that the ability of the neuraxis to produce the Obersteiner-Redlich zone is very limited temporally or topographically during embryogenesis. If the neuraxis is to construct this glial-Schwann cell barrier, the axons apparently must grow in at the right time and right place during embryogenesis. If one were to assume that the fibres in the current case arose during embryogenesis and not from a post-natal mechanism, the axons would have been wrong in their timing in reaching the vagal rootlet junction zone and wrong in their place in reaching the ligula. Otherwise the Obersteiner-Redlich zone would have formed.

SUMMARY

In 14 serially sectioned human medullae oblongata, one had peripheral nerve fibres penetrating the neuraxis. Unique features of this case are bilateral symmetry of the fibres, their poor myelination intraxially, their large, coarse axons, and the apparent absence of a predisposing lesion of the neuraxial wall. The peripheral axons traversed the neuraxial tissue in company with Schwann cell sheaths and

blood vessels. They proceeded ventrally as far as the hypoglossal nucleus. Dwindling in number as they went, the axons vanished without their mode of termination being apparent. Their origin, whether during pre-natal or post-natal life, was not clear.

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