Letters to the Editor

Hereditary demyelinating neuropathy of infancy: a genetically complex syndrome

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We read with interest the recent paper by Tyson et al. (1997). They report on nine patients with infantile hereditary demyelinating peripheral neuropathy. In two of them, nerve biopsy study revealed histological abnormalities characteristic of hereditary neuropathies with focally folded myelin sheaths (Ohnishi et al., 1989). The clinical picture they observed in these two individuals was extremely severe with involvement of both proximal and distal muscles of lower and upper limbs. The oldest patient aged 16 years was seriously handicapped and wheelchair-bound. Since both the patients’ parents were consanguineous, an autosomal recessive inheritance was presumed. The molecular study failed to demonstrate any of the mutations recently reported in hereditary demyelinating neuropathy (Raeymaekers et al., 1992; Nelis et al., 1994), namely duplication in chromosome 17p11.2–12, point mutations in the four exons of the PMP-22 or the six exons of the P0 myelin genes, or linkage to chromosome 11q23 (Gambardella et al., 1996). Conversely, in a second unrelated family originating in a small village near Crotone in southern Italy, with two siblings affected with CMT4B, we failed to demonstrate either duplication in chromosome 17p11.2–12, point mutations in the four exons of the PMP-22 or the six exons of the P0 myelin genes, or linkage to chromosome 11q23 (Gambardella et al., 1997). Moreover, Gabreëls-Festen et al. (1996) recently found different mutations on the P0 gene in three sporadic unrelated patients, whose clinical and neuropathological findings were highly characteristic of CMT4B.

Therefore, all these findings clearly indicate that the disorder of hereditary demyelinating neuropathy with focally folded myelin sheaths seems to be phenotypically quite homogeneous, but that it is genetically heterogeneous.

In this way, as stated by Tyson et al. (1997), infantile demyelinating neuropathies may be better classified by the nature of the genetic defect or chromosomal linkage if established. Genetic characterization will not only allow unambiguous diagnosis of such demyelinating neuropathies; it should also provide insight into the study of myelinogenesis.

References


Reply


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We are grateful to Professor Quattrone for his interesting comments on our patients with autosomal recessive demyelinating neuropathy with focally folded myelin. We were aware that the responsible gene had been mapped to chromosome 11 in one family, but this was published after our paper was prepared. The exclusion of linkage to chromosome 11 in another family clearly indicates genetic heterogeneity for this phenotype. We agree that the clinical picture for cases reported so far is relatively uniform, with an onset in infancy and the development of severe disability during childhood. Nevertheless, this is a nonspecific phenotype. It would not be possible to distinguish these cases clinically from children with de novo P0 or PMP22 point mutations with an onset in early childhood, although motor nerve conduction velocity, at least in our cases, was not quite as severely reduced.

The terminology used to categorize these and related hereditary neuropathies is currently very unsatisfactory. To call these patients, with a severe childhood autosomal recessive demyelinating neuropathy with focally folded myelin type 4B Charcot–Marie–Tooth (CMT) disease (Ben Othmane et al., 1993) does not equate with the clinical findings as they bear no close resemblance to the phenotype described by Charcot, Marie and Tooth. The same applies to patients with a chromosome 17p11.2 duplication, designated in the gene mapping literature as CMT 1A. A significant proportion of these patients do not show a CMT phenotype (Thomas et al., 1997). Dyck and Lambert (1968) originally introduced the designation hypertrophic neuropathy of Dejerine–Sottas type for patients with a demyelinating neuropathy with an onset in childhood with presumed autosomal recessive inheritance. This was considered to represent a homogeneous condition (Dyck et al., 1993). Even though in one of the pair of siblings originally reported by Dejerine and Sottas, the onset of the neuropathy was in adolescence, this designation was useful clinically to define a particular group of patients. However, it is now evident that most, but not all, patients with the Dejerine–Sottas syndrome have de novo dominant mutations of the P0 or PMP22 genes (reviewed by Tyson et al., 1997). A family with an autosomal dominant demyelinating neuropathy linked to chromosome 8q (Ionesescu et al., 1995) has also been described as having Dejerine–Sottas disease.

The term hereditary motor and sensory polyneuropathy was introduced by Thomas et al. (1974), later abbreviated to hereditary motor and sensory neuropathy (HMSN) by Dyck (1975), as a nonspecific designation to enable subdivision of patients with peroneal muscular atrophy and related disorders into different clinical and genetic groups pending the identification of the underlying disease mechanism, as had happened earlier for Refsum’s disease. The categorization of these conditions in terms of the particular gene mutation is now being achieved. Nevertheless, there will be problems in devising a classification that is useful both for the clinician and the geneticist. It is likely that different mutations at the same locus will give rise to variable and overlapping phenotypes. Broader designations may have to be retained for clinical purposes, whereas the precise genetic delineation will obviously be necessary for genetic counselling and prediction of disease prognosis.

The other facet of these cases with focally folded myelin that merits comment is the explanation of the morphological changes. These are not specific for autosomal recessive disorders as they have been described in a family with autosomal dominant inheritance (Umehara et al., 1993). It will be of considerable interest to establish how the different patterns of pathological change in the various hereditary demyelinating neuropathies are related to the genetic defects. Here the use of transgenic rodent models offers considerable potential. Not only are hereditary demyelinating neuropathies intriguing clinically; they may also provide valuable insights...
into the neurobiology of axon–myelin relationships in peripheral nerve (Suter et al., 1993).

References


