An Update on the Hardie Neuroacanthocytosis Series

S. Gandhi(✉), R.J. Hardie, and A.J. Lees

Abstract In 1991 Hardie described the clinical and pathological features of 19 cases of neuroacanthocytosis, resulting in the largest series reported with this rare disorder. During the past 15 years, there have been many advances in our understanding of the neuroacanthocytosis syndrome, including the identification of several different molecular causes. We have revisited the original Queen Square series in an attempt to correlate the clinical picture and natural history of each case with the new genetic findings.
1 Introduction

Our knowledge of neuroacanthocytosis (NA) represents a good example of the stages which occur in the development of understanding any rare genetic neurological disease. A distinctive clinical syndrome is first described in a number of case reports and is then followed by discoveries which shed light on the underlying molecular basis of the disease. In this chapter we use the latest developments in the field of NA and apply them to a previously well-described, and often cited clinical series of patients reported from the National Hospital for Neurology and Neurosurgery, Queen Square, London.

The original association between the haematological abnormality of acanthocytosis and a neurological syndrome was recognised in 1950 [2]. The earliest descriptions linked a neurological syndrome, acanthocytosis and an accompanying disturbance in lipid metabolism (such as abetalipoproteinaemia). From 1967, case reports of individuals and families with hereditary acanthocytosis and a neurological syndrome without lipid abnormalities also appeared [4, 5]. Finally, reports in the 1980s confirmed another association, between a rare blood group characterised by weak expression of the Kell system and absent expression of Kx antigen (described in 1961 [1]), acanthocytosis and neurological abnormalities. This X-linked genetic disorder was termed ‘McLeod syndrome’. ‘Neuroacanthocytosis’ was now divided into three broad groups consisting of (1) NA with lipid abnormalities (2) hereditary NA without lipid abnormalities (3) X-linked NA without lipid abnormalities and with the McLeod blood group.

In 1991 Hardie and colleagues reported a clinical, haematological, and pathological series of 19 patients with NA [6], consisting of 12 cases from three different families and seven non-familial cases. All cases were included in the study if they exhibited acanthocytosis, neurological symptoms or signs, and normal plasma lipoproteins. The series included two cases of the McLeod phenotype in a single family.

It was concluded that NA was a progressive disease with a mean age of onset of 32 years (range 8–62). The movement disorder was characterised by chorea, although dystonia, tics, and parkinsonism were also reported. Orofaciolingual involuntary movements were also common. Two cases had no movement disorder. Over half the patients had cognitive impairment or psychiatric features. Depressed or absent tendon reflexes were found in over two thirds, and in three cases a sural nerve biopsy confirmed a chronic axonal neuropathy. Creatine kinase (CK) levels were raised in over half of the cases. The authors concluded that there was marked phenotypic variation, and that the genetic basis for NA was probably heterogeneous.

Since the original paper was published, many developments in understanding the molecular basis of this disease have occurred. These developments have enabled us to apply genetic diagnoses to a number of the cases within it. This has the advantage of redefining a subgroup phenotype by its molecular aetiology, and also of permitting more informative genotype–phenotype correlations.