NEUROLOGICAL RARITIES

Neuroacanth

Dr Adam Zeman* and Dr Geoff Shenton†
*Consultant Neurologist and part-time Senior Lecturer, Division of Clinical Neurosciences, University of Edinburgh, Western General Hospital; †Specialist Registrar, Department of Haematology, Western General Hospital, Edinburgh EH4 2XU.
Email: az@skull.dcn.ed.ac.uk
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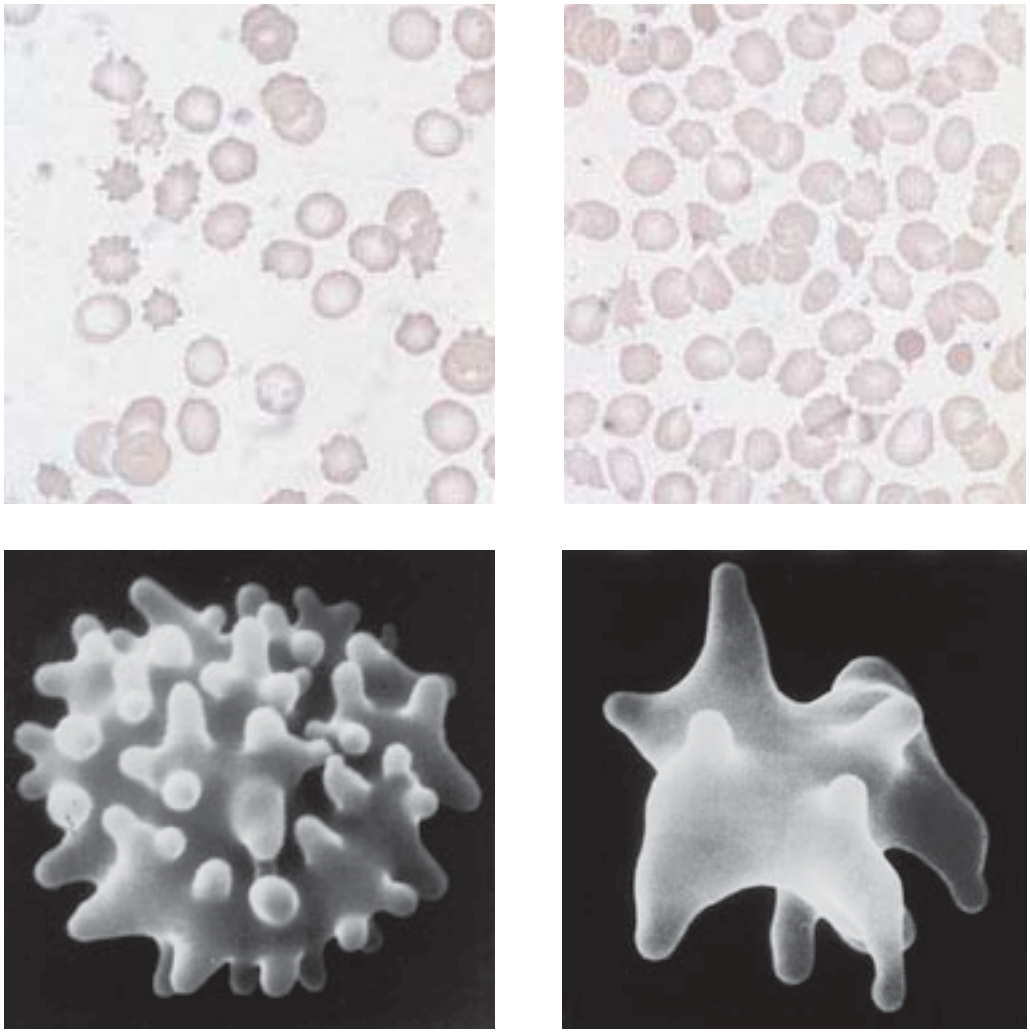

Figure 1 The appearances of echinocytes or 'burr cells' (top and bottom left) and acanthocyes (top and bottom right) on light and electron microscopy. Echinocytes and acanthocyes are easily confused on routine inspection of a blood film.

ocytosis

INTRODUCTION

Acanthocytes, from the Greek 'acantha' meaning thorn, are red blood cells with irregular thorn-like projections. They are easily confused with 'echinocytes' also known as 'burr cells', which occur in liver disease, uraemia and following splenectomy. Echinocytes have more regular projections and a broader base than acanthocytes (Fig. 1). Acanthocytes are not normally present in peripheral blood. Their detection requires careful, sometimes repeated, examination of blood smears. They are principally associated with three rare but fascinating neurological syndromes: choreoacanthocytosis, the McLeod syndrome and hypo- and abeta-lipoproteinaemia (Fig. 2).

AN ILLUSTRATIVE CASE

A 50-year-old unemployed man, who had been abnormally fidgety ever since childhood, was referred to the psychiatric services because of impulsive and disinhibited behaviour, for example going naked into his back garden and talking loudly to himself in public. He had been sleeping poorly. Furthermore, his wife reported that he been hoarding 'junk' in his house for many years. He had been sacked from his work as a chef about 10 years before because he had become too disorganized to cope. He was an only child and there was no relevant family history.

Examination revealed lack of insight into his difficulties, an inappropriately jocular manner, choreoathetosis, borderline wasting of the muscles of his lower legs and areflexia. Neuropsychological assessment did not indicate any impairment of general intelligence but suggested 'subcortical or frontal lobe dysfunction'. CT scan of the brain was reported to be normal (though in retrospect showed caudate atrophy). A wide range of other investigations, including genetic testing for Huntington's disease, gave normal results, except for a mention of 'burr cells' on a blood film and elevation of serum ALT to 168 U/L (10–40) with a normal gamma GT result. A diagnosis of 'frontal lobe dementia' was suggested.

However, repeated examination of blood films 3 years after his first presentation revealed the presence of acanthocytes. Creatine kinase was raised at 1350 U/L (24–161), with LDH raised at 1139 U/L (208–508). Subsequent blood grouping demonstrated the McLeod phenotype with weak expression of Kell group antigens (see below). The diagnosis was confirmed by genetic testing. Levels of apolipoprotein B were normal. The final diagnosis was neuroacanthocytosis due to the McLeod syndrome. His behavioural disturbance has progressed, requiring compulsory detention under the Mental Health Act.

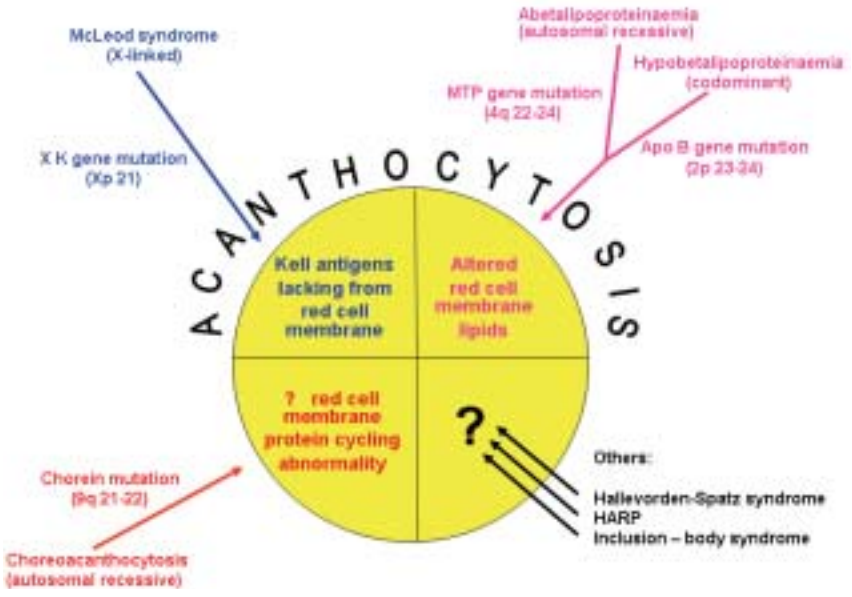

Figure 2 The causes of neuroacanthocytosis, showing their genetic basis and the mechanisms by which they cause acanthocytosis.

VARIETIES OF NEUROACANTHOCYTOSIS

The terminology is confusing. We have followed recent practice by referring to the group of neurological disorders associated with acanthocytes collectively as 'neuroacanthocytosis' (Rampoldi *et al*. 2002). The underlying relationships of the conditions within this group have been clarified by the identification of their genetic basis (Fig. 2).

Choreoacanthocytosis and the McLeod syndrome

These disorders belong together because they are phenotypically similar, although genetically distinct (Danek *et al*. 2001; Stevenson & Hardie 2001; Rampoldi *et al*. 2002). Both present most commonly in adult life with motor, cognitive and psychiatric features:

- The motor disorder is usually chorea, but dystonia, tics, involuntary vocalizations and parkinsonism also occur. There is often associated dysarthria and sometimes dysphagia. Tongue and lip biting are described, particularly in choreoacanthocytosis.
- Epilepsy occurs in around 50% of people with either condition.
- The pattern of cognitive impairment is 'fronto-subcortical', with predominant impairment of executive functions (planning, initiation, self-monitoring and self-correction of thought and behaviour), although mild-moderate general intellectual decline can occur.
- Psychiatric features include 'personality change' with socially inappropriate behaviour, depression, anxiety, emotional lability, obsessive-compulsive disorder, hoarding and occasionaly psychotic symptoms.
- An axonal peripheral neuropathy is a feature of both conditions, with areflexia occurring commonly and associated peripheral muscle wasting and weakness in some cases. True myopathy is confined to the McLeod syndrome in which a cardiomyopathy, seen in around two thirds of patients, is a common cause of death.
- Splenomegaly and hepatomegaly can occur.
- The McLeod syndrome is distinguished by the presence of a generally well-compensated haemolytic anaemia, and weak expression of Kell antigens on red blood cells: the Kell group of erythrocyte antigens is the third most important blood group system after the ABO and rhesus systems.
- Neuroimaging reveals abnormalities in the basal ganglia in both conditions, with atrophy and signal change affecting the caudate, putamen and globus pallidus. SPECT and PET scanning indicate reduction of blood flow, glucose utilization and dopamine-receptor binding in the striatum.
- Post-mortem studies confirm the impression that these disorders target the basal ganglia, and provide no evidence for direct involvement of the cerebral cortex.

The affected genes have now been identified. Choreoacanthacytosis is an autosomal recessive condition, while the McLeod syndrome is X-linked. The gene implicated in the former, on chromosome 9, codes for a protein known as *chorein*, which is expressed widely in human tissues. The numerous mutations described in the chorein gene *may* cause acanthocytosis by affecting the passage of proteins into the red cell membrane. The mechanism by which neurones are lost from the basal ganglia is unknown, but likely to be due to a local effect of the gene in the striatum rather than to red cell acanthocytosis *per se*. In the McLeod syndrome the affected gene, XK, on the X chromosome, codes for the *XK* protein which anchors Kell antigens in the red cell membrane. Local expression of the gene in brain, nerve and muscle, rather than red cell acanthocytosis *per se*, probably accounts for the neurological manifestations.

Table 1 Neurological disorders associated with red cell acanthocytosis

Choreoacanthocytosis
McLeod syndrome
Hypo- and abeta-lipoproteinaemia
Hallevorden-Spatz disease
Autosomal dominant disorder associated with chorea, dementia, parkinsonism, acanthocytosis and ubiquitin-positive cortical inclusion bodies
HARP syndrome (hypo-prebeta-lipoproteinaemia, acanthocytosis, retinitis pigmentosa, pallidal degeneration)

Hypo- and abeta-lipoproteinaemia

Abeta-lipoproteinaemia is characterized by a spinocerebellar syndrome, fat malabsorbtion, and acanthocytosis in the peripheral blood (Rampoldi *et al*. 2002). The neurological features include progressive peripheral neuropathy with dorsal column sensory loss, cerebellar signs and retinitis pigmentosa. Fat malabsorbtion is

suggested by failure to thrive and steatorrhea. Triglyceride and cholesterol levels, and levels of fat-soluble vitamins, are very low. Serum apolipoprotein B is absent. Onset is usually in childhood but can occur in young adults. Though rare, it is important to recognise the condition because neurological deterioration can be prevented by treatment with Vitamin E. Hypo-abeta-lipoproteinaemia has a similar though more variable and generally milder phenotype, but a distinct mode of inheritance and genetic basis. The neurological features also respond to Vitamin E.

Abeta-lipoproteinaemia is an autosomal recessive disorder (Rampoldi *et al*. 2002). It is caused by mutations in a gene on chromosome 4q22–24 that codes for 'MTP', a microsomal triglyceride transfer protein. Hypo-beta-lipoproteinaemia is an autosomal codominant condition generally caused by mutations of the apolipoprotein B gene itself on chromosome 2p23–24: heterozygotes are usually asymptomatic. The acanthocytosis associated with both disorders is thought to be due to an abnormal lipid composition which lowers the fluidity of the red cell membrane.

OTHER NEUROLOGICAL DISORDERS ASSOCIATED WITH RED CELL ACANTHOCYTOSIS

Several other, even rarer, neurological disorders have been associated with acanthocytosis (Rampoldi *et al*. 2002). These include a recently described autosomal dominant disorder associated with chorea, dementia, parkinsonism, acanthocytosis and ubiquitin-positive cortical inclusion bodies (Walker *et al*. 2002); some cases of Hallevorden-Spatz disease, which is now known to be due to mutations in the panthothenate kinase gene; and the HARP syndrome (**h**ypo-prebeta-lipoproteinaemia, **a**canthocytosis, **r**etinitis pigmentosa, **p**allidal degeneration).

AND SO?

These syndromes are all uncommon, though of course significant to those who suffer from them. Choreoacanthocytosis and the McLeod syndrome are mimics of Huntington's disease; abeta- and hypo-beta-lipoproteinaemia are treatable inherited disorders. Diagnosis requires a diligent hunt for acanthocytes by a forewarned and interested haematologist. This family of disorders illustrates the extraordinarily rapid progress of neurogenetics, which has brought order to a confusing area of neurology by identifiying almost all the responsible genes within the last decade, although a good deal more work is required to trace every link in the chain from gene to behaviour. These conditions defy the misleading distinctions we all tend to draw between psychiatric, neurological and general medical disorders. In a similar vein, they highlight the complex functions of the basal ganglia: the caudate, putamen and globus pallidus contribute to cognitive and behavioural as well as to motor processes (Cummings 1993). Besides chorea, dystonia and parkinsonism, striatal pathology is apt to give rise to personality change, depression, mania, obsessive-compulsive disorder and subcortical dementia.

CONCLUSIONS

- Acanthocytes are very easily confused with echinocytes (burr cells) in the peripheral blood – haematologists need to be asked specifically to distinguish them.
- Acanthocytes are associated with a number of rare neurological disorders, particularly choreoacanthocytosis, McLeod syndrome and hypo and abeta-lipoproteinaemia.
- Hypo- and abeta-lipoproteinaemia respond to vitamin E.
- McLeod syndrome and choreoacanthocyotsis are easily confused with other disorders such as Huntington's disease and have genetic implications for affected families.
- Disorders of the basal ganglia – the primary site of pathology in choreoacanthocytosis and McLeod syndrome – can present with cognitive and psychiatric symptoms and signs, as well as with motor features.

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