Scientific Commentary

Action myoclonus–renal failure syndrome: the definitive clinico-pathological description

The causes of myoclonus are protean and often obscure; none more obscure than the action myoclonus–renal failure (AMRF) syndrome reported in four French Canadian patients from the province of Québec by Andermann et al. in 1986. In their current paper, Andermann and colleagues transform this condition from a local rarity to one of global significance, identified in families from Canada, the USA, Cuba, Europe and Australia (Badhwar et al., 2004). Patients in their series presented in the second and third decades of life with renal, neurological or combined features. Tremor was usually followed by the development of progressively disabling myoclonus on voluntary movement, coupled with cerebellar signs, infrequent generalized seizures, but preserved cognitive function. Renal disease presented as proteinuria and progressed to renal failure. Renal biopsy revealed collapsing glomerulopathy, a severe variant of focal segmental glomerulosclerosis that is more commonly seen in the setting of human immunodeficiency virus infection. Without treatment, death occurred 12 years or so after onset of the first symptom. Brain autopsy in two patients revealed extra-neuronal pigment accumulation. Segregation analyses were compatible with autosomal recessive inheritance.

The common onset of AMRF with a fine tremor may lead to particular difficulties in diagnosis, and deserves further comment. The EEG finding of spike and spike–wave complexes and the evolution of the tremor into an action myoclonus make it likely that the early tremor is a variant of the relatively recently recognized cortical tremor syndrome (Ikeda et al., 1990). Although phenomenologically dominated by tremor, the latter is accompanied by cortical hyperexcitability indistinguishable from that in cortical myoclonus, and is commonly seen in the setting of epilepsy (Guerrini et al., 2001). Thus giant cortical evoked potentials, time-locked cortical correlates and excessive cortico-muscular coherence would be anticipated in AMRF and have been confirmed in a British sibship (Brown and Omerod, unpublished results).

One of the major contributions of Andermann and colleagues has been to demonstrate that dialysis and renal transplantation are effective treatments for the renal failure, extending the lifespan in a disorder without cognitive involvement. Nevertheless, treatment of renal failure does not afford associated improvement in the neurological syndrome, which requires symptomatic therapy with antimyoclonic agents such as levetiracetam.

The combination of myoclonus and renal failure raises an interesting differential diagnosis. It may be a direct consequence of uraemic encephalopathy, reversible with dialysis or transplantation, or have a more specific cause. Dialysis encephalopathy is caused by aluminium toxicity and is characterized by speech disturbance, seizures and myoclonus. It is at least partially reversible if treated with complete absence of oral aluminium intake and elimination by desferrioxamine. Drug toxicity in renal failure may also present with myoclonic encephalopathies (Martinez et al., 2001). The above causes are usually associated with some disturbance of conscious level, which is not the case in AMRF or in the rare May and White syndrome of myoclonic ataxia and deafness, which may also be associated with nephropathy, diabetes mellitus, infrequent seizures and dementia. Although familial, it is likely to be a mitochondrial cytopathy as abundant ragged red fibres may be found on muscle biopsy (Vaamonde et al., 1992). Finally AMRF should be distinguished from the rare Galloway–Mowat syndrome, an autosomal recessive disorder, usually of infantile onset and associated with proteinuria, focal segmental glomerulosclerosis, microcephaly and cerebellar disease.

The pathological findings in the AMRF syndrome afford no direct clue as to the likely nature of the dysfunction within the CNS. No significant loss of cerebral cortical cells was seen. Paradoxically, relatively pure syndromes of cortical tremor and cortical myoclonus are usually associated with discrete cerebellar cortical disease, often with disproportionate loss of granule cells (Tijssen et al., 2000). The latter may lead to diminished excitation of Purkinje cells, release of the cerebellar nuclei from tonic inhibition by Purkinje cells and consequent increased excitation of the cerebral motor cortex and cortical myoclonus or tremor (Tijssen et al., 2000). The cerebellar signs and atrophy in AMRF also implicate the cerebellum in this condition, but granule cells were not explicitly mentioned in the account of Badhwar et al. (2004). On the other hand, pigment deposits were prominent in the Bergmann astrocytes of the cerebellar cortex, damage to which may cause a relatively selective secondary loss of granule cells (Cui et al., 2001).
In the current issue of *Brain*, Andermann and colleagues succeed in defining the AMRF syndrome and highlighting it as a cause of progressive myoclonic ataxia across many continents. The extent to which it has been under-recognized and misdiagnosed as uraemic encephalopathy remains to be seen.

PETER BROWN
Sobell Department of Motor Neuroscience and Movement Disorders
Institute of Neurology
University College London
London, UK

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