Ion Channel Research in the Institute of Neurology Results in a National and International Diagnostic Service for Previously Undiagnosed Patients with Neurological Channelopathies.

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Many important neurological diseases are episodic and affected patients experience attacks of unpredictable severe neurological dysfunction separated by periods of apparent normality. The commonest episodic neurological disorders are epilepsy and migraine but their precise molecular pathophysiology is an important unsolved neuroscience challenge. Over the past twelve years a world-leading collaborative clinical, genetic and cellular electrophysiological research programme in the Institute of neurology has progressed fundamental understanding of the pathophysiology of episodic neurological diseases. This research has been translated into clinical practice with clear positive patient impact. The group have systematically studied families in which episodic brain or muscle dysfunction is inherited. They have shown that mutations in critical ion channel genes are the central cause. These disorders are now known as the neurological channelopathies—a term that was little known 12 years ago but is now familiar to clinical neurologists, thanks in part to the national diagnostic service the group developed at Queen Square.

The joint clinical-genetic research investigators have collated one of the world’s largest cohorts of over 1000 families with inherited channelopathies and have identified 100’s of unique mutations in specific genes responsible for the diseases. The molecular electrophysiological consequences on single ion channel function have been studied using detailed cellular expression techniques allowing a more precise understanding of the underlying pathophysiology. Many key observations have been made. For example, they have shown that mutations in important presynaptic neuronal potassium and calcium channels can lead to episodic ataxia—a disorder characterised by profound disabling attacks of unpredictable unsteadiness. Furthermore, they have shown that such patients are 17 times more likely to develop epilepsy compared to the background population risk. In addition, by studying large groups of patients with different intermittent muscle symptoms they have been able to show how genetic dysfunction of muscle sodium, potassium, calcium or chloride channels can relate to specific episodic muscle conditions including periodic paralysis, muscle stiffness syndromes (myotonia) and episodic cardiac arrhythmias. The group have also defined previously unrecognised neonatal ion channel diseases including intermittent hyoptonia and stridor—knowledge of which can avoid unnecessary tests in the neonatal period.

This research has lead directly to the UK government funded national ion channel clinical genetic and electrophysiological diagnostic service which has had an important impact on the lives of a previously often undiagnosed group of patients. Patients with neurological channelopathies were often misdiagnosed as psychogenic disorder or there was an unacceptably long delay in achieving a diagnosis. This service is unique world-wide and now receives large numbers of international referrals. The innovative investigative patient pathway combines clinical assessment and specialised electrophysiological analysis to direct DNA-testing with a linked diagnostic cellular molecular expression service to determine if newly identified mutations are pathogenic. New treatments are being tested in large multicentre NIH and MRC funded treatment trials now in progress in the UCL MRC Centre for Neuromuscular Disease.


