JOURNAL WATCH

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Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of neurodegenerative disease management.

Expert panel: Kaviraja Udupa, Division of Neurology, Department of Medicine, University of Toronto, ON, Canada; Susan H Fox, Division of Neurology, Department of Medicine, University of Toronto, ON, Canada; Theresa A Zesiewicz, University of South Florida, FL, USA; Duncan McLauchlan, Cardiff Brain Repair Group and MRC Centre for Neuropsychiatric Genetics & Genomics, School of Medicine, Cardiff, UK

Tilma J, Tilma K, Norregaard O, Ostergaard JR. Early childhood-onset restless legs syndrome and effect of oral iron treatment. *Acta Paediatr.* 102(5), e221–e226 (2013).

Restless legs syndrome (RLS) is a common neurologic disease in adults. Characterized by an unpleasant urge to move the legs, typically at night or during periods of inactivity, RLS is a common cause of sleep disruption, which may result in social, occupational and educational impairment. The diagnosis of RLS is made subjectively, assisted by the International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria and questionnaire.

What happens when RLS patients, such as children, cannot vocalize their symptoms? Night time waking is very common in children. Due to underdeveloped language skills, children may not be able to describe the unpleasant urge to move their legs that profoundly interferes with sleep, which can even cause daytime behavioral issues. Sleep disruption in children may also be mistakenly attributed to causes other than RLS, and be treated as such.

In the study by Tilma *et al.*, symptoms of RLS were found to start as early as the first year of life, and were accompanied by low ferritin levels and a high Periodic Limb Movement Index during Sleep (PLMSI). The symptoms were reduced with iron supplementation. The authors studied 22 children who had been referred to a pediatric clinic for a variety of symptoms, including bronchiolitis, night time crying and sleep disturbance. While the children had no

problems falling asleep, they all woke up during the night, the majority after 1–3 h, kicking and screaming. Fourteen of the patients described leg ‘pain’; the eight children who could not vocalize their symptoms kicked and jerked their legs. Baseline ferritin levels were recorded in 20 of the 22 children, with a median level of 21 ng/ml (range: 5–42). Following oral iron treatment, the median level was 59 ng/ml (range: 18–123). In children who experienced RLS symptom improvement with iron supplementation, the median ferritin value was 65 ng/ml (range: 38–123). Polysomnography testing corroborated positive PLMSI of more than 5 h in all 14 children who received the test. Thirteen out of the 22 children also had a history of RLS in a first-degree relative.

Greater awareness of RLS in children, even infants, is important for parents and healthcare providers. Serum ferritin levels should be drawn in children suspected of suffering from RLS, with the consideration of iron supplementation in children with serum ferritin levels under 50 ng/ml.

– Written by Theresa A Zesiewicz

Cui G, Jun SB, Jin X *et al.* Concurrent activation of striatal direct and indirect pathways during action initiation. *Nature* 494(7436), 238–242 (2013).

The basal ganglia provide information to the cortex to coordinate movement. This information is channeled through two pathways that have classically been thought

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to be separate with respect to dopamine receptor function. The so-called 'direct' pathway is excited by dopamine D1 receptors and activates movement, while the 'indirect' pathway is inhibited by dopamine D2 receptors and reduces movement. This then gives us a simple basal ganglia model with which to predict changes that will occur in movement disorders, such as Parkinson's disease, and the effect of treatment with dopaminergic agents [1–3].

However, the recent study by Cui *et al.* challenges this concept of functional dichotomy between the direct and indirect pathways [4]. They used a novel technique of fiber optics technology in transgenic mice models. The authors used genetically encoded calcium indicators in the striatum – either direct (D1-*Cre*) or indirect (A2A-*Cre*) – to differentiate these two pathways. This advanced optogenetic technology allowed quantification of the neuronal activity in these two pathways in freely behaving animals. They measured activity in these two pathways while the mice performed a task of pressing bars and collecting food pellets. The main finding was concurrent activity of both direct and indirect pathways during activity, with both pathways being relatively silent during the resting state. This finding, therefore, questions the established concepts of reciprocal activation of these two pathways in active and resting states.

Although this new concept of coordinated activity of both the direct and indirect striatopallidal pathways is interesting, more work needs to be performed to confirm the findings. Translation into primate brains is of key importance to establish whether this concept also holds true in the human brain. Investigating the coordinated activity of these two pathways in Parkinson's disease and other basal ganglia disease models with hypo- and hyper-kinetic movement disorders is crucial. Nevertheless, this new technique and findings open up novel ways of investigating the pathophysiology of basal ganglia neurodegenerative movement disorders and potential therapeutic strategies.

– Written by Kaviraja Udupa
& Susan H Fox

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Evans SJ, Douglas I, Rawlins MD, Wexler NS, Tabrizi S, Smeeth L. Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. *J. Neurol. Neurosurg. Psychiatry* doi:10.1136/jnnp-2012-304636 (2013) (Epub ahead of print).

The prevalence of Huntington's disease (HD) has been estimated to be approximately six per 100,000 based on surveys of hospital, general practice surgeries and nursing home records. However, these have probably been underestimates given the stigma surrounding the condition (and hence reluctance to inform general practitioners or record HD in practice records), lack of a confirmatory gene test in earlier studies, and the less typical phenotypes now recognized and diagnosed as HD (for example 'senile chorea'). In 2010, Rawlins noted the marked discrepancy between prevalence estimates and the number of patients referred to the Huntington's Disease Association [1]. The present study attempted to address the discrepancy by using a cohort drawn from a large range of general practice surgeries over a 20-year period, looking for patients with adult-onset HD.

This study used the general practice research database – a cohort of 625 practices across the UK with over 5 million anonymized patients. Diagnoses are recorded by a 'read code' for the purposes of general practice reimbursement; prior

work has demonstrated high diagnostic accuracy. Read codes for HD were 'Huntington's chorea' and 'dementia in HD', and patients registered with a general practice surgery and aged 21 years or over between 1990 and 2010 were included in the study. A selection of records for other choreiform disorders were also reviewed at random to see if a diagnosis of HD could be made retrospectively. Point prevalences were calculated for each year.

A total of 1136 patients (544 men) were diagnosed with HD, with an average prevalence of ten per 100,000 for the 20-year period. The prevalence markedly increased over the years, from 5.4 in 1990 to 12.3 in 2010. The prevalence was highest in northern England and Scotland, and lowest in London (England). By this estimate, 5700 individuals in the UK have adult-onset HD; a figure much closer to the Huntington's Disease Association's records of 6702 service users in 2010.

Intriguingly, reassessment of the records of 115 patients (from a total of 566) coded as 'other chorea' suggested a possible diagnosis of HD in 14 cases based on associated psychiatric features and lack of an alternative explanation for chorea.

This study provides an estimated prevalence much closer to that suggested by referrals to the Huntington's Disease Association, and is unlikely to represent overdiagnosis given the availability of a gene test and the necessity for specialist assessment prior to genetic testing. The most accurate prevalence estimates could be gained by prospective laboratory records, correlated with clinical assessment, but the time and resources involved would probably prove prohibitively expensive. The increasing prevalence over time may reflect improved diagnostic accuracy, but may also be due to improved treatment, in particular the recognition and management of early suicidality and poor nutrition.

– Written by Duncan McLauchlan

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Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a

financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert

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s.freeston@futuremedicine.com