Dopamine transporter (DAT) deficiency, a recessive disorder due to mutations in the encoding SLC63 gene, was first described by Kurian et al. (2009, 2011). The typical phenotype originally reported was infantile dystonia-parkinsonism with a characteristic metabolic profile in the CSF, namely a raised homovanillic acid:5-hydroxyindoleacetic acid (HVA:5-HIAA) ratio, usually in excess of 4.0. Presynaptic DAT, expressed by dopaminergic neurons, is responsible for reuptake of extracellular dopamine in a Na+/Cl−-dependent manner (Torres et al., 2003). In this issue of Brain, Ng et al. (2014) describe a new cohort of patients with dopamine transporter deficiency syndrome (DTDS) and evaluate the functional consequences of SLC6A3 mutations using in vitro heterologous expression.

The clinical significance of this paper is the new phenotypic associations. In addition to the classical presentation—infantile-onset progressive parkinsonism-dystonia—Ng et al. (2014) report cases who presented atypically, later in childhood and with a milder disease course. The new cohort consisted of eight cases with a median age at diagnosis of 13 years; one patient was diagnosed at 34 years. All eight patients had either homozygous or compound heterozygous nonsense or splice site mutations in the SLC6A3 gene.

Three of eight cases, from one kindred, had juvenile onset progressive parkinsonism-dystonia. Notably, all three brothers had a normal birth history and neonatal course, and achieved normal early developmental milestones in infancy. At 10–11 years of age, they all developed a tremor affecting the head, with progression of symptoms in their 20s. Another case, despite having infantile-onset, survived into his fourth decade.

Ng et al. (2014) also present evidence for dysfunction of the DAT gene in the new cases. In vitro studies of mutant transporter showed several defects in dopamine transporter function, including absent or reduced dopamine uptake, reduced DAT cell surface expression, and reduced affinity for dopamine. Loss of post-translational dopamine transporter glycosylation and failure of amphetamine-mediated dopamine efflux were also detected. The degree of dysfunction was greater for mutations causing infantile-onset than for those causing juvenile-onset disease. For example, the A314V mutation associated with atypical DTDS exhibited the highest residual dopamine uptake capacity compared with the mutations causing infantile DTDS.

This report expands the phenotypic spectrum of DTDS, which includes presentation in infancy (early onset, rapidly-progressive disease), and in childhood/adolescence (later onset, slower disease progression). Genotype–phenotype analysis in this cohort, consistent with several other enzymatic recessive disorders, suggests that the higher residual dopamine transporter activity contributed to postponing disease presentation or slowing down progression in these late-onset cases.

What is the significance of this report for clinicians, in particular paediatric neurologists and movement disorders specialists? DTDS is probably under-recognized. To date, apart from the original report (Kurian et al., 2009, 2011), there has been only one other study describing similar early-onset cases (Henriksen et al., 2012), and overall there are only a handful of cases in the literature. This study highlights the need to consider DTDS in the differential diagnosis for both infantile- and juvenile-onset movement disorders presenting with tremor and dystonia-parkinsonism. Some of these cases may be masquerading as cerebral palsy or other conditions that present with juvenile dystonia and parkinsonism (Schneider and Bhatia, 2010). Given that some of the patients with DTDS have oculogyric crises, other disorders in the dopamine synthesis pathway such as tyrosine hydroxylase deficiency and sepiapterin reductase deficiency enter into the differential diagnosis. Moreover, because tremor was common, juvenile parkinsonism needs to be kept in mind, particularly due to parkin gene mutations. However, in this regard, the DAT SPECT scan is normal in DTDS, whereas most cases of degenerative juvenile parkinsonism, including those arising from parkin gene mutations, will have an abnormal DAT scan. Hence the combination of the CSF analysis, showing a raised HVA/HIAA ratio, and a normal DAT scan, should be a clear pointer for DTDS, which of course can be confirmed on genetic testing.

Finally, it is interesting to note that the cases described by Ng et al. (2014) are not only from an Asian background, but also include Italian and mixed European ancestry, and it is likely that these conditions are present in all countries. The message for clinicians is, when faced with a patient with infantile or adolescent dystonia-parkinsonism, even if presenting in adulthood, don’t forget to consider ‘that DAT’ gene.

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Is PTEN hyperactivity behind poor regeneration in diabetic neuropathy?

Neuropathy is a troublesome complication of diabetes mellitus that commonly affects the sensory and autonomic nervous systems. Impaired nerve conduction and axonopathy lead to pain and/or paraesthesia followed by sensory loss. There is no effective treatment for diabetic neuropathy, in part because its mechanisms are poorly understood. Research has focused on correcting the changes induced by hyperglycaemia, such as oxidative stress, glycation of macromolecules, and mitochondrial dysfunction (Tomlinson and Gardiner, 2008). Neuroprotective strategies that target neurons, Schwann cells, and nerve blood supply have also been suggested (Calcutt et al., 2008) but none have been successful (Apfel, 2002; Ropper et al., 2009). However, in this issue of Brain, Douglas Zochodne and colleagues present evidence that inhibition of the phosphatase PTEN (phosphatase and tensin homolog) can produce functional improvements in a mouse model of diabetic neuropathy (Singh et al., 2014).

A frequent consequence of diabetic neuropathy, in addition to nerve degeneration, is the failure of axons to regenerate after injury. Recent studies of axon regeneration in the CNS have focused on the phosphatase PTEN. PTEN dephosphorylates the signalling lipid phosphatidylinositol-3,4,5-trisphosphate (PIP3) at position three. PIP3 mediates growth factor receptor signalling (including that of insulin) through activation of PI3-kinase at the plasma membrane. Activation of PTEN thus reduces activity in critical signalling pathways that promote growth and survival downstream of PIP3, such as those mediated by activated Akt/PI3K and mTOR, while activating antagonistic signals (such as GSK3β and FoxO transcription factors). PTEN is a tumour suppressor, but patients with inactivating mutations in PTEN can also present with seizures, learning disability and other neurological symptoms (van Diepen and Eickholt, 2008). Notably, deletion or knockdown of PTEN increases CNS neuron survival and axon regeneration after injury (Park et al., 2010). PTEN is also expressed in dorsal root ganglion (DRG) neurons (Chadborn et al., 2006) and mediates growth cone collapse and decreased axon elongation, suggesting that PTEN inhibition may also enhance nerve regeneration in the PNS.

In a previous study, Zochodne and colleagues examined whether inhibition of PTEN could regenerate a decline in a rat model of sciatic nerve injury (Christie et al., 2010). They showed that PTEN knockdown improved regeneration, and that this effect was additive with the beneficial effect of a preconditioning lesion. Following nerve transection, pharmacological inhibition or knockdown of PTEN by short interfering RNA delivered to the injury site accelerated axon outgrowth in vivo. In the present paper, Zochodne’s group ask whether PTEN might also restrict nerve regeneration in a mouse model of diabetes. The first surprise to emerge from the data is that PTEN messenger RNA and protein expression are substantially increased in sensory neurons in two murine models of diabetes, a type 1 model induced by streptozotocin (STZ) (which depletes insulin by causing rapid pancreatic B cell death), and a type 2 model, the db/db mouse. Sciatic nerve crush injury further increased PTEN messenger RNA in the DRG neurons of diabetic mice compared with injured control mice, although no protein increase above that induced by STZ itself was present 3–6 days after injury.

Singh et al. (2014) then examined functional outcomes after nerve injury in non-diabetic and STZ-treated mice. The latter had confirmed type 1 diabetes and diabetic neuropathy as indicated by elevated blood glucose, reduced weight gain, impaired motor and sensory nerve conduction and loss of sensation to mechanical and noxious stimuli. PTEN knockdown increased motor conduction velocity and compound motor action potentials in the diabetic mice, as well as sensory nerve conduction velocity. These effects were less notable in the injured nerves of control animals. In addition, PTEN knockdown increased both the number and the diameter of myelinated fibres in the tibial nerve of the diabetic mice, increased sensory fibre density in the footpad, and partially restored the response to a noxious mechanical stimulus. As each of these were initially reduced by 50–70% in the diabetic mice compared with control animals, STZ itself was present 3–6 days after injury.

It is less clear whether PTEN elevation in diabetic mice compared with control animals, the effects of PTEN short interfering RNA were especially clear in the diabetic mice. Although not all parameters were significantly improved, this partial functional recovery in a model of diabetic neuropathy is a promising start. Whether the beneficial effects persist beyond the 28 days examined by Singh et al. (2014) remains to be seen.