

DYT1 Dystonia

Primary Young-onset Dystonia and the DYT1 mutation

Primary dystonia is defined as the presence of dystonia as the only symptom (with or without tremor), with no clear secondary cause and no neurodegeneration. Patients with primary dystonia with onset before the age of 25 tend to develop limb dystonia which often generalises, but tends to spare the head and neck. This pattern has been referred to by many names over the years: primary torsion dystonia, dystonia musculorum deformans, Oppenheim's dystonia. In 1997, Ozelius and colleagues identified a mutation in the DYT1 gene on chromosome 9q in about 70% of patients with this young-onset primary dystonia phenotype.¹

The DYT1 Mutation and its cellular consequences

The DYT1 mutation is a single GAG deletion that causes the loss of a glycine residue close to the ATP-binding end of the protein torsin A.¹

The function of torsin A is unknown. It is widely expressed throughout the body and in the brain is mainly localised to the dopaminergic neurons of the substantia nigra, and also the hippocampus.² Torsin A is an endoplasmic reticulum-bound protein³ and forms part of the AAA+ superfamily of ATPases (ATPases with a variety of cellular Activities). Torsin A is hypothesised to form a six membered ring structure, and may serve a chaperone function, for example in the folding or unfolding of proteins,⁴ perhaps including those involved in dopamine release from vesicles.⁵ Over-expression of wild-type torsin A appears to protect cultured cells from toxic insults. As *in vivo* evidence of this cellular protection function, torsin A has been identified as a component of Lewy bodies.⁶

When mutant torsin A is over-expressed in cell cultures, inclusion bodies form within the cells consisting of 'whorls' of mutant protein.⁷ Pathological studies of the brains of those with DYT1 dystonia are in general normal,⁸ but inclusion bodies within cholinergic neurons in the brainstem of DYT1 mutation carriers have recently been reported.⁹

DYT1 Dystonia: Inheritance and Phenotype

DYT1 dystonia is inherited in an autosomal dominant fashion, but with markedly reduced penetrance. Only 30-40% of mutation carriers ever develop dystonia, and in those that do, almost all develop symptoms before the age of 25.¹⁰

Typical age at onset is in late childhood or early-teens. Dystonia almost always starts in a limb, and then spreads to affect other limbs. The head, neck and bulbar structures are rarely affected. The degree of eventual spread is very variable between patients, ranging from

isolated hand dystonia to severe generalised dystonia.^{10,11}

Spread of symptoms usually occurs over two to four years after onset, and then symptoms will stabilise. Minor fluctuations of symptom severity may then occur, and secondary problems (eg. scoliosis) may develop later, but late-development of dystonia in a previously unaffected body part is rare.¹⁰

The differential diagnosis in DYT1 dystonia is not usually extensive. Most patients with secondary/hereditary degenerative dystonia will have other symptoms and signs apart from dystonia, or the dystonia will be of a pattern that would be unusual for primary young-onset dystonia (eg. cranial/bulbar involvement). Of course, such additional symptoms and signs may not be present at the onset of the dystonia. Two important differentials in this regard are dopa-responsive dystonia and young-onset Parkinson's disease. It is also important to remember that the DYT1 mutation only accounts for a proportion of those with the 'Oppenheim dystonia' phenotype, and there are a number of patients who are DYT1 negative, but nevertheless have a typical DYT1 phenotype.

The pathophysiology of DYT1 dystonia

Electrophysiological and functional imaging investigation of those with DYT1 dystonia has identified a number of deficits in inhibitory motor pathways in the brain, brainstem and spinal cord.^{12,13} These are similar to the abnormalities found in patients with other forms of primary dystonia (eg. torticollis).¹⁴ Interestingly, similar abnormalities of cortical motor function are found in carriers of the DYT1 mutation who do not have dystonia.¹² Such abnormalities are therefore not sufficient on their own to cause dystonia. There is increasing interest in the idea that an excessive ability to undergo plastic change in the motor system may underlie the development of primary dystonia in general. There is some limited evidence that this may also be the case for DYT1 mutation carriers who manifest dystonia, but that carriers without dystonia may have less ability to undergo plastic change than normal subjects.

Guidelines for Diagnostic Testing

Diagnostic testing guidelines have been published for DYT1 dystonia.¹⁰ It is suggested that diagnostic testing be performed in those with primary dystonia who have onset below the age of 26. Testing of those with onset after 26 is only recommended if there is a family history of typical young-onset primary dystonia. Gene testing is technically straight-forward, and is commercially available.

Treatment of DYT1 Dystonia

Until the advent of deep brain stimulation surgery (see



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below), the mainstay of treatment was with medication and in some cases botulinum toxin.

Most patients receive a trial of levodopa. This helps to exclude the possible diagnosis of dopa-responsive dystonia as the cause of the symptoms, and also, a small minority of patients with DYT1 dystonia can have a partial response to levodopa.

Anticholinergic drugs are still the mainstay of medical treatment for DYT1 dystonia. Trihexyphenidyl should be introduced very slowly. Patients should aim for the highest tolerated dose: young patients can sometimes reach very high doses (up to 100mg per day) with good benefit on symptoms if titration is slow. However, many patients reach the point

of unacceptable side effects long before a useful impact on symptoms occurs.

Other medical treatments (often used in combination) include benzodiazepines (eg. clonazepam), tetrabenazine and baclofen. For severely affected patients, a popular strategy in the past has been to use a 'triple therapy' of anticholinergic, benzodiazepine and dopamine receptor blocking drugs.

Botulinum toxin injections have a limited role in those with DYT1 dystonia. If a particular functional problem can be identified (eg. dystonic spasm of the dominant hand causing inability to write), then treatment with botulinum toxin may be indicated. However, for those with generalised symptoms there are often too many muscles that require treat-

ment for injections to be of benefit.

Lesion operations of the basal ganglia (eg. pallidotomy) were previously used in those with DYT1 dystonia, with some success, but also side effects. In recent years, deep brain stimulation of the internal segment of the globus pallidus (GPi), has emerged as a very promising therapeutic option for those with DYT1 dystonia. Improvement of dystonia of 70-95% is typical in those treated with GPi stimulation, and the improvement appears to be sustained (over at least five years of follow up so far).¹⁵ The operation does carry acute (eg. haemorrhage) and long term (eg. lead infection, fracture) complications, but overall within a specialist centre, results are highly consistent.

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