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Two cases of autosomal recessive generalized dystonia in childhood: 5 year follow-up and bilateral globus pallidus stimulation results

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SUMMARY

We report two brothers with an unknown form of early-onset familiar dystonia. Characteristic clinical features are (1) childhood-onset; (2) extrapyramidal motor symptoms; (3) dysarthria; and (4) mental retardation. Additional findings include loss of D_2-receptors in both basal ganglia and hypoplasia of the cerebellar vermis with dilatation of the fourth ventricle and cisterna magna. There seems to be a progressive and non-progressive form of this clinical entity. Dystonic symptoms of the progressive form that occurred in one of the brothers were alleviated dramatically by bilateral internal globus pallidus (Gpi) stimulation, and the improvement has lasted now for 5 years.

1. Introduction

Dystonia is a movement disorder characterized by involuntary sustained muscle contractions, often leading to twisting and repetitive movements or abnormal postures.[1] Distinction can be made between primary and secondary forms. In primary dystonias no underlying cause can be identified. A genetic classification of primary dystonias has been replacing the clinical one, as more gene loci have been discovered.[2] Seven different gene loci have been identified in autosomal dominant dystonias (i.e. in primary torsion dystonia (9q34),[3,4] focal dystonia (18p),[5] adult-onset primary torsion dystonia of mixed type (8p21–p22),[6] dopa-responsive dystonia (14q22.1–q22.2),[7,8] paroxysmal dystonic choreoathetosis (2q25–q33; 1p13.3–p21),[9–11] and myoclonus dystonia (7q21; 18p11)).[12,13] Two loci have been found in X-linked recessive forms (i.e. in the X-linked dystonia parkinsonism syndrome (Xq13.1)[14,15] and in X-linked sensorineural deafness, dystonia, and mental retardation (Xq22)).[16] Two other autosomal dominant dystonias can be distinguished on clinical grounds. No gene loci have been identified yet. These dystonias are paroxysmal dystonia (kinesigenic choreoathetosis)[17,18] and rapid onset dystonia parkinsonism.[19–21]

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The tentative DYT4 locus was assigned to several autosomal dominant forms of dystonia in which DYT1 was excluded.[2,22–25] In all probability, future genetic analysis will reveal the disease genes involved.

The existence of autosomal recessive forms of dystonia has never been proven, although it is still suggested in a few Gypsy families.[26]

Dystonias can also be secondary to birth injury, trauma or other neurological diseases (such as Wilson's disease, Huntington's disease, Parkinson's disease, Hallervorden–Spatz disease,[27] multiple sclerosis, stroke), or occur as a side effect of drugs.

We present two brothers with a previously not reported form of early-onset dystonia, in one of whom bilateral pallidal deep brain stimulation was performed. Both patients have been followed for 5 years.

2. Methods and results

Patients 1 and 2 are brothers born from non-consanguineous parents of non-Jewish origin. There is a negative family history for dystonia. Both parents and the eldest son are not affected.

2.1. *Case 1*

Patient 1 is the middle of three brothers. Pregnancy and perinatal course had been normal. At the age of 10, he suddenly developed lateroflexion of head and trunk to the right side, followed by involuntary movements of the trunk and in a lesser extent of the arms. Levodopa/benserazide medication in a low dose appeared to improve the symptoms, and after stopping this medication the patient was free of symptoms for 1 year. Then dystonic symptoms reappeared for 3 months and were treated again with levodopa/benserazide with a partial effect. After a symptom free interval of 9 months dystonia reappeared after a sinusitis. Symptoms were progressive and consisted of spinal torsion to the left side, torticollis to the right, equinovarus of the right foot, dysarthria, walking difficulties with a falling tendency to the left, and an intention tremor in the right hand. During one and a half year he was treated with levodopa/benserazide (up to 250 mg/day) and bromocriptine (up to 10 mg/day). This had a positive beneficial response. The following years dystonic symptoms recurred occasionally, mostly elicited by periods of illness and stress. At present the patient is 27 years of age, medication free, and the sole remaining symptom consists of a slight torticollis to the right side.

Laboratory investigations were normal for CSF and blood, including serum copper and ceruloplasmin. T1- and T2-weighted magnetic resonance imaging (MRI) revealed a mild hypoplasia of the cerebellar vermis with a widened fourth ventricle and cisterna magna. There were no abnormal signal intensities. An IBZM-SPECT-scan showed a substantial loss of D_2-receptors in both basal ganglia. Psychological examination revealed an IQ-score of 85.

2.2. *Case 2*

Patient 2, the youngest of three brothers, had a history of Perthes' disease and icterus when he showed first symptoms of dystonia at the age of 11. Pregnancy, perinatal course and developmental milestones had been normal. From the age of 5 he started to have learning difficulties and was sent to a school for mentally retarded children. The first symptoms of dystonia started in the right foot and progressed to the left foot and right wrist. Over years he developed a severe and devastating lordosis and torsiscoliosis of the thoracolumbar spine. Speech became dysarthric. Symptoms did not aggravate in the evening, but disappeared during sleep and were only mild after arousal.

Neurological examination revealed walking difficulties due to hypertonic muscles of the lower extremities, equinovarus of both feet and hyperextended toes. Knee tendon reflexes were brisk, but no Babinski signs were elicited. There was a flexion contracture of the right wrist. His back was arched owing to dramatic lordosis; his spine also showed a severe kyphoscoliosis. Speech was dysarthric and there was a nystagmus. At fundoscopy no abnormalities were seen. Vision was normal.

Extensive laboratory investigations, including serum ceruloplasmin, did not reveal any hematological abnormalities. T1- and T2-weighted MR images showed widening of the fourth ventricle and cisterna magna; signal intensities of the basal ganglia were normal (Fig. 1).

Cortical magnetostimulation revealed normal latent periods to muscles of upper and lower extremities. A muscle biopsy was negative for mitochondrial myopathy. Chromosome investigations were normal. The disease locus DYT1 was excluded. Extensive investigations and consultation by international experts did not lead to a definite diagnosis.

Therapeutic trials included trihexyfenidyl (up to 8 mg/day), diazepam (up to 5 mg/day), paravertebral botulinum toxin-injections, levodopa/benserazide (up to 375 mg/day), baclofen, apomorfine and clozapine (37.5 mg/day). All medications had little or no effect, except for apomorfine that improved symptoms temporarily when given in a low dosage.

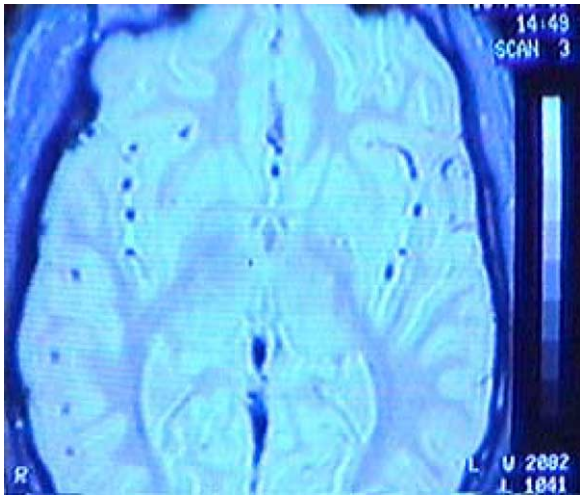

Fig. 1 – T2-weighted inverse recovery MR image showing widening of the fourth ventricle.

At age 18 the patient was not able to sit or walk anymore, due to hyperextension of the thoracolumbar and cervical spine. Because of total exhaustion we decided for a pentothal induced coma at the Intensive Care Unit. Attempts to treat dystonia with transdermal nicotine patches were not successful. Lowering of the daily dosage of diazepam led to an aggravation of dystonic symptoms. Finally, he was discharged from the ICU with the following medications: tetrabenazine (75 mg/day), pimozide (4 mg/day) and trihexyphenidyl (6 mg/day).

Because the patient was severely invalidated, especially by his extreme lordosis, we decided for bilateral internal globus pallidus (Gpi) deep brain stimulation.

The pre-operative Fahn–Marsden Scale was 90 (BFM: Movement Scale). Pre-operative medication consisted of tetrabenazine (75 mg/day) and trihexyphenidyl (6 mg/day). In October 1999, at the age of 19 he was admitted to hospital and after application of a stereotactic Fisher–Leibinger headframe, a CT-scan was made under general anesthesia to determine the coordinates of the anterior and posterior commissures for estimation of the targetpoints. The patient was transferred to the operating room. Under general anesthesia without using muscle relaxants, two burr holes were made on both sides 2 cm anterior of the coronary suture and 2.5 cm lateral of the midline. The targetpoints in the internal globus pallidus were determined from the coordinates of the anterior and posterior commissures. The targetpoint normally used in Parkinson's disease was chosen: 2 mm in front of mid AC-PC, 5 mm below AC-PC and 21 mm lateral of AC-PC (head width 16 cm, third ventricle width 8 mm, AC-PC 25 mm long). A Fisher TCU 002 unipolar radiofrequency electrode 1.0 mm in diameter with a 3.0 mm exposed tip was inserted until 8 mm above target. Test stimulations were performed at 2 and 100 Hz up to 4 V. Stimulation electrodes were moved forward in 2 mm steps and test stimulations were repeated. Irritation of the internal capsule was generated on target on both sides at 3.8 V, which was manifest in flexion spasms of the arms. Stimulation electrodes were removed and replaced by stimulation leads (Medtronic model 3387) that were inserted until on target. Leads were fixed by plastic burr hole caps. Efferent ends of the leads were rolled up and placed in subcutaneous pockets. Wounds were closed on both sides and the stereotactic head frame was removed. Retro-auricular and subclavicular incisions were made on both sides. Stimulators (Medtronic Itrell II) were placed in subcutaneous pockets under both clavicles. The stimulators were subcutaneously connected to the leads by extension cables.

Postoperative confirmation of the position of the electrodes in the GpI with MRI could not be obtained. This is because in The Netherlands it is not allowed to obtain MRI's of patients with cerebral implanted leads because of possible cerebral complications caused by heath production as a result of the MRI. However, to illustrate the feasibility of positioning of such an electrodes in the GpI, in Fig. 2 an MRI is shown of this type of electrode in the GPi in a patient from another European country. The Medtronic 3387 lead measures 10.5 mm in length between the lower edge of contact zero and the upper end in contact 4. This fits within the Gpi provided the orientation of the electrode is orthogonal with the entry burrhole about 2.5 cm from the midline. Probably the uppermost contact is at the upper border of the Gpi abutting GPI.

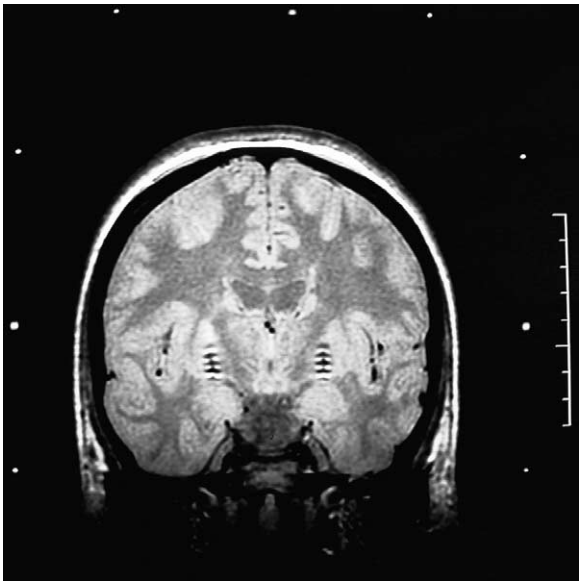

Fig. 2 – Example of an MRI showing Medtronic 3387 lead electrodes positioned in the GPi. This MRI was obtained from a patient from another European country because as a result of legislation in The Netherlands, we could not obtain it from the patient described in this report.

One day after operation both stimulators were set and switched on. The following stimulation parameters were used on both sides: contact 0, 1, 2 and 3 negative, case positive (unipolar) 3.3 V, pulse width 60 μs, frequency 140 Hz, thus creating areas in the brain comparable with pallidotomy in Parkinson's disease. Gpi stimulation had a nearly direct effect on myoclonias which disappeared completely. Apart from that there was only little improvement.

Six weeks postoperatively there was obvious improvement of muscle tone and spasms, but a complete correction of functionality was not observed. Although there still was equinus of both feet, the spine was no longer arched. The patient was able to walk short distances, turn around in bed and walk stairs. We also noticed an improvement in the patient's mood.

Eight months after operation he still showed further improvement. He was able to sit straight in a chair and to sit on the floor with his knees extended, something that had been impossible for many years.

The Fahn–Marsden (BFM) Scale: Movement Scale was 68.

2.3. *Long-term evaluation*

Two years after implantation the battery of the left stimulator was depleted and resulted in a torsoscoliosis of the right side of his body. After replacement of the left stimulator this one-sided torsoscoliosis disappeared instantly. During the 5 years follow-up we replaced the pulse generators two times. During the last revision the Itrells were replaced by Kinetras (Medtronic) with the aim to double the life time of the pulse generators.

During the follow-up there has been no worsening of the symptoms. Currently, he is able to walk unaided for distances up to 500 m. His hand function is still slowly improving.

Before operation the patient was constantly at home, being under his mother's care. Nowadays he functions more independently. The Fahn–Marsden Scale has remained 68.

3. Discussion

Symptoms of dystonia may begin during childhood, in adolescence or during adulthood. In early-onset dystonia symptoms usually start in the foot or in the hand and may spread to the trunk and the rest of the body, resulting in generalized dystonia. Often early-onset dystonia is caused by a mutation in the DYT1 gene on the long arm of chromosome 9 (9q34) leading to primary torsion dystonia (PTD)[3,4], or by a mutation in the gene for GTP-cyclohydrolase 1 at chromosome 14q22.1–q22.2 leading to dopa-responsive dystonia.[7,8] Rare forms of early-onset dystonia include rapid onset dystonia-parkinsonism[19–21] and dystonias that are part of neurodegenerative disorders like Wilson's and Hallervorden–Spatz disease.[27]

We presented two patients with respectively a mild and a severe form of early-onset dystonia. Although extensive investigations have been made, no definite diagnosis could be given. Because of a similar presentation of symptoms and a negative family history the cause resembled a hereditary, autosomal recessive disorder. Existences of autosomal recessive forms of dystonia however have not been demonstrated. In the past, most forms suggestive of autosomal recessive dystonia appeared to be of autosomal dominant origin with reduced penetrance.[2] However, an autosomal recessive mode of inheritance has been suggested in a few Gypsy families.[26]

Common features observed in our patients, included (1) childhood-onset, (2) extrapyramidal motor symptoms, alleviated by sleep and elicited by periods of stress, (3) dysarthria, and (4) mental retardation. Additional findings comprised of loss of D_2-receptors in both basal ganglia and hypoplasia of the cerebellar vermis with dilatation of the fourth ventricle and cisterna magna.

In patient 1, the first symptoms occurred in the neck and trunk and followed a non-progressive course. In patient 2, dystonic symptoms began in the lower extremities after which a rapid generalization took place, leading to severe exhaustion and invalidity. This clinical picture is also seen in primary torsion dystonia (PTD), and cases of generalization of dystonia when the first symptoms occur in the lower extremities.[28] However, PTD could not be confirmed because genetic analysis was negative for DYT1. Other forms of early-onset primary dystonia, such as dopa-responsive dystonia and rapid onset dystonia-parkinsonism, were excluded on clinical grounds. In case 1, there may have been some dopa-responsiveness, but there was a long remission without medication. In case 2 with severe dystonia, nystagmus, dysarthria, mental retardation and hypertonic lower extremities without Babinski signs, there was no beneficial dopa response. Instead levodopa even worsened the dystonia. Wilson's disease was excluded by laboratory investigations.

Many symptoms also reflect the characteristics described in Hallervorden–Spatz syndrome, but this was not supported by abnormal signal intensities of the basal ganglia on T2-weighted MR images or abnormalities at fundoscopy. Also, the spontaneous improvement of patient 1 does not support Hallervorden–Spatz disease.[29]

General dystonias refractory to medical treatment may be considered for surgical intervention. Thalamotomy mainly reduces distal limb dystonia and has a minor effect on truncal symptoms. Pallidotomy has a considerable effect on all dystonic symptoms. During these operations deep brain structures, involved with the initiation and generation of movement, are destroyed in an attempt to 'rebalance' movement and posture control. Recently, deep brain stimulation has been introduced as a treatment for cervical and general dystonia.[30–36] Continuous electrical stimulation of the globus pallidus mimics the positive effects of pallidotomies. Also stimulation-induced complications are reversible, and stimulation parameters can be adjusted to minimize complications and maximize therapeutic effects.[34,37] Concerning the stimulation parameters there seem to be differences between pallidal stimulation in dystonia and pallidal stimulation in Parkinson's disease in which a human body topography can be observed starting proximally with the foot and ending distally with the hand. In non DYT1 dystonia the target area seems to be different in shape and function. Our results indicate that in this case a larger field including, possibly also including other pallidal areas, need to be stimulated at higher voltages. Thus, pallidal human body topography may play a different role in stimulation in dystonia compared to Parkinson's disease. A similar observation was done in a patient with tardive dyskinesia and dystonia. More research on this topic is needed.

3.1. *Concluding remark*

The cases presented here are a type of primary early-onset dystonia that have not been described before. There seems to be a progressive and non-progressive form of this clinical entity. Dystonic symptoms of the progressive form were alleviated dramatically by bilateral stimulation of the globus pallidus with resulting improvement of functionality.

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