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Benign Hereditary Chorea: Clinical and Neuroimaging Features in an Italian Family

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Video



Abstract: Benign hereditary chorea is an autosomal dominant disorder characterized by early onset nonprogressive chorea, caused by mutations of the *thyroid transcription factor-1 (TITF-1)* gene. Clinical heterogeneity has been reported and thyroid and respiratory abnormalities may be present. We describe 3 patients of an Italian family carrying the S145X mutation in the *TITF-1* gene with mild motor delay, childhood onset dyskinesias, and subtle cognitive impairment. A child in the third generation presented with congenital hypothyroidism and neonatal respiratory distress. Imaging studies in 2 patients showed mild ventricular enlargement and empty sella at magnetic resonance imaging and hypometabolism of basal ganglia and cortex at 18-Fluoro-2-deoxy-glucose positron emission tomography. © 2010 Movement Disorder Society

Key words: benign hereditary chorea; *thyroid transcription factor-1*; congenital hypothyroidism; MRI; FDG-PET

Benign hereditary chorea (BHC) is an autosomal dominant disorder characterized by childhood onset chorea with little or no progression into adult life. Mental deterioration does not occur, but slightly lower I.Q. scores have been reported. Mutations in the *thyroid transcription factor-1 (TITF-1)* gene on chromo-

Additional Supporting Information may be found in the online version of this article.

Elena Salvatore and Luigi Di Maio contributed equally to the study, and both should be considered as first authors.

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some 14q have been identified as causative in several families, most of them recently reviewed.^{1,2} A second locus (8q21) for BHC has been recently mapped in two Japanese families with adult onset chorea.³

The *TITF-1* gene is a homeodomain-containing transcription factor essential for the organogenesis of lung, thyroid, and basal ganglia.⁴ Thus, it is not surprising that the clinical spectrum in families carrying *TITF-1* mutations includes thyroid and lung disorders, such as congenital hypothyroidism and respiratory distress. The putative mechanism of disease results from gene haploinsufficiency and reduced protein product.

We previously described molecular and functional data of the novel *TITF-1* S145X mutation in an Italian pedigree.⁵ Here, we report in detail the clinical features and the neuroimaging data of the family.

CASE REPORTS

This three-generation family shows three affected individuals, one for each generation, all carrying a previously unreported mutation of the *TITF-1* gene. The genetic defect and the molecular mechanisms have been described in the previous article.⁵ The index patient was Patient 1, who had been referred for exclusion of Huntington's disease (HD). The information that her father (Pt. 2) had abnormal movements and that her son (Pt. 3) had congenital hypothyroidism led to the clinical suspicion of BHC and to the molecular analysis of the *TITF-1* gene.

Patient 1, 26 years old, began walking at the age of 18 months, but she was clumsy and fell repeatedly. Her gait much improved around puberty. Mild generalized choreic movements appeared at the age of 7 years and remained stable thereafter. No mental or behavioral abnormalities were present, she did not encounter difficulties at school, and she was graduated at a Hotel school. During puerperium, when she was 19 years old, her chorea worsened and she presented with a postpartum psychosis, characterized by depression and aggressiveness toward the newborn and successfully treated with risperidone and lamotrigine.

At the age of 23 years she was admitted to our hospital. Neurological examination showed generalized choreic movements (video) and was otherwise normal. Neuropsychological evaluation demonstrated long term verbal memory deficit and low-normal score at Raven Matrices test.

Molecular analysis of HD gene and laboratory testing were normal, a part from elevation of thyroid-stimulating hormone.⁵ Thyroid hormone replacement was started. Brain magnetic resonance imaging (MRI)

revealed ventricular dilatation, more marked in the posterior part of lateral ventricles (Fig. 1a-c) and partial empty sella (Fig. 1d). Brain 18-Fluoro-2-Deoxy-Glucose Positron Emission Tomography (FDG-PET) showed slight relative hypometabolism of the caudate nuclei and of the medial frontal and temporo-parietal cortices (Fig. 2). The patient was treated with tetrabenazine up to 75 mg daily, with mild improvement. At the age of 26 years she withdrew the therapy abruptly and presented marked worsening of chorea, irritability, emotional lability, poor sleep, inappropriate dress, and behavior. She was admitted to our hospital again, treated with quetiapine, 75 mg/daily, and discharged improved after a week.

Patient 2, the proband's father, 56 years old, had meningitis at the age of 6 months. Subsequent motor development was delayed with walking starting at the age of 5 years and normal language skills. His school performances were poor. Since childhood, slight, sporadic, hyperkinesias were present, which mainly involved the abdomen and had been stable over time. He did not report improvement by alcohol. He worked as a school-caretaker and had a normal social life. At examination jerky abdominal movements were evident; mild and rare choreic movements were present in other body regions (video). Neuropsychological evaluation showed short term verbal and spatial memory deficit, slight attentional deficit, and constructive apraxia.

Thyroid hormone screening showed primary hypothyroidism with increased TSH and mildly reduced FT3. Brain MRI evidenced slight, asymmetrical ventricular dilatation, more marked in the right side and in the posterior part of lateral ventricles (Fig. 1e-g), and complete empty sella (Fig. 1h). FDG-PET demonstrated relative hypometabolism of basal ganglia, more prominent in the caudate nuclei, and a slight relative hypometabolism of the left temporo-parieto-occipital cortex (Fig. 2). Tetrabenazine, up to 50 mg daily, was prescribed, but the drug was withdrawn for insomnia and nervousness.

Patient 3, the 5 years old proband's son, born at term by cesarean delivery because of transverse position, received continuous positive airway pressure therapy for neonatal respiratory distress. The infant presented with multiple congenital anomalies: severe bilateral vesicoureteral reflux with pyelectasis and megabladder, patent foramen ovale, and congenital hypothyroidism for which thyroid replacement treatment was started.

Psychomotor development was delayed: sitting at 10 months, walking at 26 months, first words at 26 months, at present only few words in vocabulary and lack of sphincter control. His I.Q. was 76 at the age of

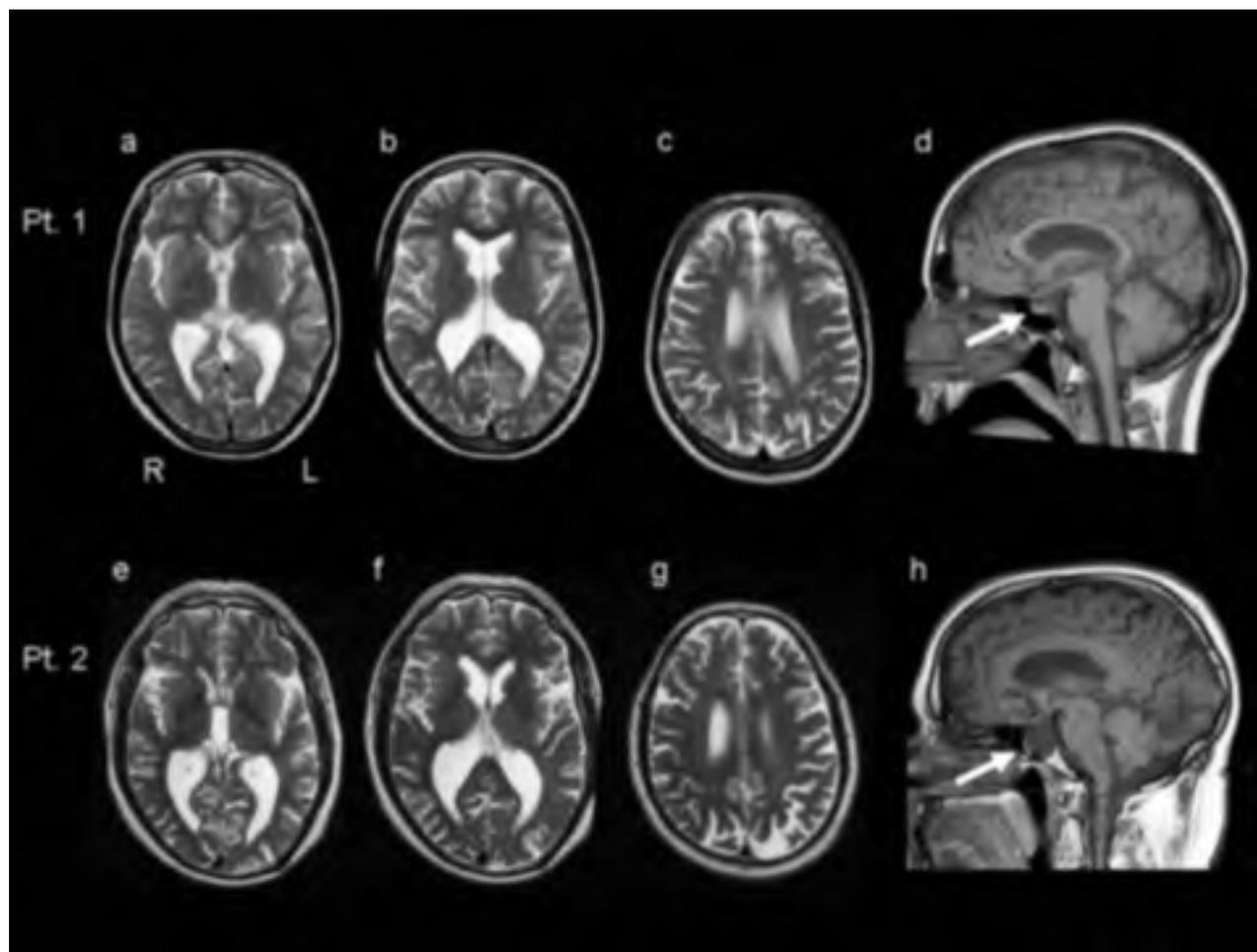


FIG. 1. Axial T2-weighted (Pt. 1 a–c; Pt. 2 e–g) and sagittal T1-weighted (Pt. 1 d; Pt. 2 h) MR images. Dilatation of supratentorial ventricular system is evident in both patients. Enlargement of the third ventricle is also evident in Patient 2. In both patients there is evidence of empty sella, partial in Patient 1, complete and prominent in Patient 2.

4 years. He is a pleasant boy, has no behavioral problem and developed normal social relationships. At the age of 4 years he developed slight, generalized choreic movements (video).

Molecular analysis: Direct sequencing of the *TITF-1* gene showed, in all the 3 patients, the new heterozygous mutation C609A in exon 2, resulting in a substitution of serine at codon 145 for a stop codon (S145X). The mutation predicted a truncated protein of about 14.5 kDa that lacks the entire homeodomain and the carboxy-terminus portion.⁵

DISCUSSION

BHC shows heterogeneity of the clinical presentation within and among the families. In the present family the neurologic presentation, characterized by mild

motor delay, early-onset dyskinesias, and slightly lower intelligence, was quite similar in the 3 patients, although the abnormal movements are somewhat different among individuals. Although chorea is the movement disorder characteristic of BHC, dystonia, myoclonic jerks, and ataxia have been also described.⁶ The distinction among chorea, myoclonus, and jerky dystonia may be difficult. The diagnosis of chorea, which is characterized by a random flow of rapid, unpredictable abnormal movements,⁷ better applies to Patients 1 and 3, whereas the sudden, more predictable and repetitive abdominal jerks in Patient 2 seem to be more consistent with myoclonus. As described in other patients with BHC,⁶ dyskinesias, contrary to myoclonus-dystonia, were not worsened by action nor improved by alcohol.

Concerning extra-neurologic features subclinical hypothyroidism was present in Patients 1 and 2, whereas

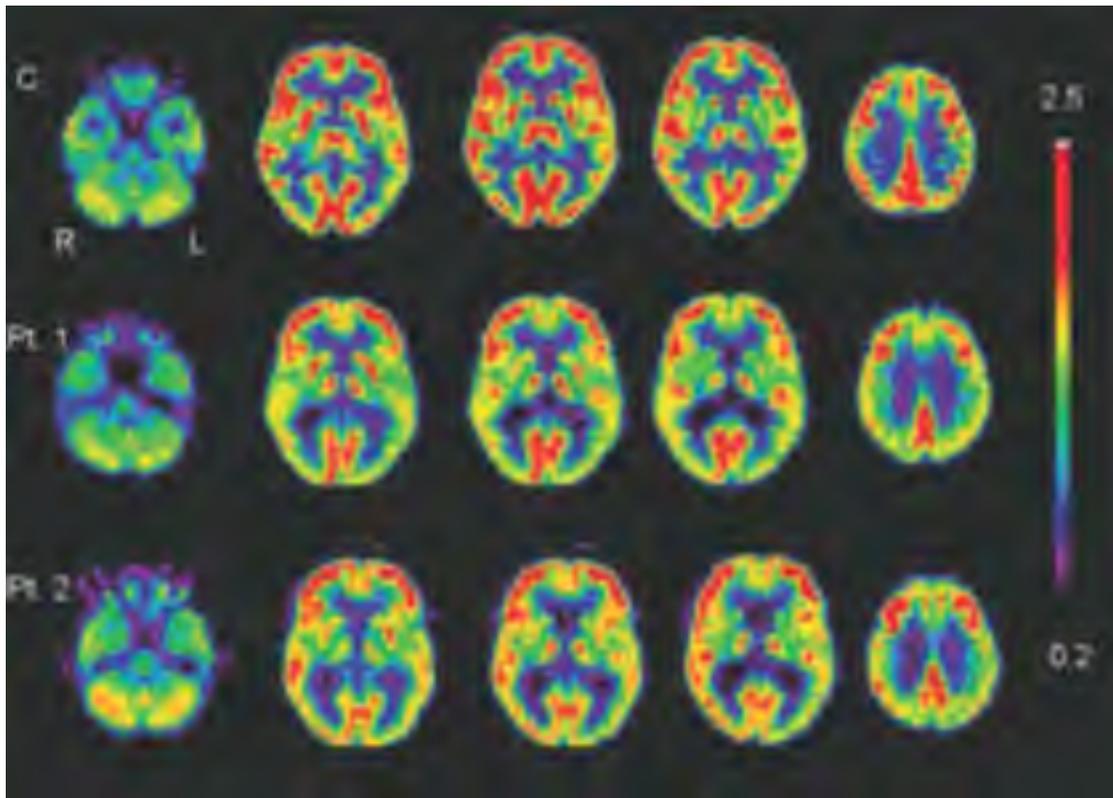


FIG. 2. Axial images of brain ^{18}F -deoxy-glucose uptake obtained with PET in a 39 years control, in Patient 1 and in Patient 2. The images were spatially normalized into the Montreal Neurological Institute (MNI) space and normalized to globals. The scale shows values of highest uptake in red and lowest uptake in blue. In Patient 1 a mild reduction of tracer uptake is present in the caudate nuclei and in the medial frontal and temporo-parietal cortex, bilaterally. The basal ganglia hypometabolism is more marked in Patient 2, involving more the caudate than the putamen regions. In Patient 2 there is also a mild temporo-parietal metabolism reduction on the left side. L left, R right.

Patient 3 had congenital hypothyroidism and neonatal respiratory distress. Anticipation and more severe phenotype in subsequent generations have been suggested,⁸ but not demonstrated in BHC. Environmental factors and genetic background might also influence the clinical expression. A review of the reported cases^{1,2,6,9–16} reveals 11 cases of congenital hypothyroidism due to *TITF-1* mutations in patients with de novo mutations or with no information about parental phenotype or genotype, 11 (including the present one) with maternal inheritance of the allele carrying the mutation, and one with paternal inheritance.¹⁶ However, there are also reports of maternal inheritance without congenital hypothyroidism. The predominance of maternal inheritance of congenital hypothyroidism in BHC may be due to chance or may be related to imprinting or maternal environment.

It remains unclear if some peculiar features of our patients, as postpartum psychosis in Patient 1 and urinary tract malformations in Patient 3, are related to the mutation. Psychosis occurred in two previously reported patients^{16,17} and hypospadias has been described before

recognition of the molecular defect.^{18,19} We are not aware of a role of *TITF-1* in urinary tracts organogenesis, although the gene is expressed in small cell carcinoma of the urinary bladder.²⁰ We suggest special attention to urinary tract malformations in patients with BHC.

Imaging data also appear to be heterogeneous in BHC. CT/MRI findings are usually normal, but ventricular dilatation and other abnormalities have been also reported.^{10,21,22} A cystic mass in the posterior part of the sella turcica has been described in two cases.²² In the 2 patients investigated by us, MRI showed ventricular dilatation, more evident at trigone and occipital horn level, whereas in HD ventricular enlargement mostly affects the frontal horns.²³ Empty sella was present in both patients, more marked in Patient 2, which has the longest disease duration. Haploinsufficiency of the *TITF-1* gene could lead to congenital deficiency of the sellar diaphragm, which is a frequent cause of an enlarged sella. FDG-PET scan was reported to be normal in 4 patients with BHC,⁹ although a study performed when the molecular diag-

nosis was not available showed caudate hypometabolism.²⁴ More recently reduction of technetium 99 m ethyl cysteinate dimer uptake has been demonstrated in the basal ganglia of two children studied by SPECT.²⁵ Using FDG-PET we showed cortex and basal ganglia hypometabolism in both Patient 1 and Patient 2. These findings are consistent with the significant reduction of striatal and neocortical interneurons demonstrated by immunohistochemical staining in BHC²⁶ and with the patients' choreic syndrome and mild cognitive impairment. The pattern of metabolic changes is similar, but less severe than that found in HD,²³ consistently with the milder, non progressive BHC phenotype.

Legends to the Videos

Segment 1. Patient 1 examination shows generalized, moderate to marked, choreic movements involving the face, the neck, the trunk, the limbs, both proximally and distally. Finger-to-nose and walking do not worsen the abnormal movements. Mild unsteadiness is also evident.

Segment 2. Slightly staggering gait and mild limb choreic movements, not worsened by action, in Patient 2. Brisk abdominal wall contractions are evident.

Segment 3. In Patient 3 mild choreic movements involved the trunk and the four limbs, both proximally and distally, not worsened by action. Brisk myoclonic-like movements are also evident. Tottering was probably too marked for his age.

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Long-Term Effect of Unilateral Pallidotomy on Levodopa-Induced Dyskinesia

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Abstract: Unilateral pallidotomy has been effectively used to treat parkinsonism and reduce levodopa induced dyskinesia (LID). We sought to determine the long-term effects of pallidotomy on LID in 10 patients who had initial benefit from pallidotomy but went on to require DBS surgery for symptom progression. The Dyskinesia Rating Scale (DRS) was used to rate and quantify LID in a blinded fashion. Though sample size was small, there was a trend towards a reduction in LID lasting up to 12 years suggesting that posteroventral pallidotomy may provide sustained benefit in reducing LID. © 2010 Movement Disorder Society

Key words: Parkinson's disease; pallidotomy; dyskinesia

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In the era before DBS, as well as currently, in many countries around the world, unilateral postero-ventral pallidotomy as a treatment for Parkinson's disease (PD) has been the surgical alternative of choice. Pallidotomy ameliorates parkinsonism and is particularly effective in reducing levodopa-induced dyskinesia (LID) most prominently in the contralateral hemibody.¹ Despite initial control of disabling symptoms, parkinsonism generally worsens several years following pallidotomy and many patients have subsequently undergone STN DBS when their symptoms again became resistant to medical regimens.^{2–4}

No long-term follow-up studies have blindly evaluated the persistent effects of unilateral pallidotomy on LID. It has been our personal experience that the anti-dyskinetic effects may be evident many years after the original surgery and Hariz reported that these effects could last up to 13.5 years.⁵

We sought to determine the long-term effect of pallidotomy on dyskinesia in a selected sample of patients who had previously undergone pallidotomy and were undergoing preoperative evaluation for STN DBS due to symptom progression. Given the extensive preoperative assessment for DBS, ON/OFF evaluations were available for review in these patients. We evaluated efficacy of pallidotomy on dyskinesia by comparing contralateral and ipsilateral dyskinesia at the STN-DBS preoperative evaluation. We postulated that there would be a difference between sides due to lasting effects of pallidal lesioning with less severe dyskinesia contralateral to the previous surgery.

PATIENTS AND METHODS

Patient Population

Ten patients (8 male) with PD and prior pallidotomy on average 7.3 years (range 2–12 years) earlier were evaluated for consideration of STN DBS. All patients were felt to have obtained an initial good response to pallidotomy with respect to parkinsonism and particularly LID. Not all patients had received pallidotomy at our center; pre and postoperative LID scores were available in 6 of the 10. Before DBS patients were evaluated under the protocol of the Core Assessment Program for Intracerebral Transplantation⁶ (CAPSIT) before STN DBS surgery. Dyskinesia was assessed using the Dyskinesia Rating Scale (DRS) (maximum score for unilateral limbs = 8). The dosage of anti-parkinsonian medication required by the patient was recorded; levodopa equivalent doses (LED) were calculated in a manner described elsewhere.⁷ Evaluations