A Not So Benign Family Pedigree With Hereditary Chorea: A Broader Phenotypic Expression or Additional Picture?

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Abstract

NKX2-1 mutations have been usually associated with a non-progressive neurological disease. Recent reports revealed a vast variability regarding its clinical expressivity. Aim of this work was widening the Benign Hereditary Chorea neurological, cognitive and behavioral phenotype through the description of a child and her family pedigree. Molecular analysis focused on *NKX2-1* gene revealed a novel frameshift mutation in the three-generation members described. Cognitive scales detected a relevant developmental delay, and the clinical observation and Autism Diagnostic Observation Schedule -2 administration allowed the diagnosis of autism spectrum disorder in the proband. Microarray testing, further executed to exclude a double hit contextually provoking the complex neurodevelopmental disorder, revealed the 22q11.2 Duplication Syndrome. This paper may contribute to enlarge Benign Hereditary Chorea variable expressivity and, together with other studies reported in the literature, underlines the need to reconsider the term "benign," verifying the opportunity of more a complex diagnosis.

Background

Benign hereditary chorea (BHC, MIM 118700) is a rare multisystemic disorder with autosomal dominant inheritance. Its more frequent presentation is a childhood-onset movement disorder manifesting with chorea or even, rarely, with dystonia, tremor, myoclonus and ataxia,[1,2] that usually has no or minimal progression into adulthood. Its most characteristic presentation symptom is motor delay associated with random flow of rapid abnormal movements, not rhythmic or stereotypical, unpredictably involving many different parts of the body at different times. Cognitive function is typically normal or slightly below the norm[1,2] and it helps to differentiate BHC versus other choreas (i.e. Huntington's disease, chorea-acanthocytosis), though at least a portion of cases are found to have reduced Intelligence Quotient (IQ).[3,4]

Far from being a pure neurological disorder, the clinical spectrum of BHC is associated with hypothyroidism and respiratory disease in approximately 30-50%,[4] composing a triad known as the "brain-lung-thyroid" syndrome.

BHC is a highly phenotypically heterogeneous disorder, both due to the variable combinations of lung, thyroid, and neurological abnormalities, and the different intrafamilial clinical presentations. Choreic movements, in fact, greatly vary, ranging from infrequent and hardly detectable to severely

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choreic movements that interfere even with simple motor tasks and become debilitating. Sometimes, symptoms improve with age.[1]

Neurologically unusual manifestations, peculiar brain imaging findings and microcephaly,[1,5–7] and some dysmorphic features have also been described.[6] A psychiatric phenotype (including depression, psychosis, obsessive-compulsive disorder, and attention deficit hyperactivity disorder-ADHD) has also been reported in different families.[4,6,8]

The first BHC pedigree[9] suggested the autosomal dominant mode of transmission. Mutations in *TTF1* gene (also named *TITF1*, *TEBP* or *NKX2-1)* on chromosome 14q13, implicated in the morphogenesis of thyroid, lung and brain, causes BHC, although mutations in *ADCY5* have also been recently detected in quite different neurological and extraneural phenotypes.[10] *NKX2-1* encodes the thyroid transcription factor-1 and it seems to play a role in striatal interneurons and cholinergic neurons of the basal ganglia.[11] In BHC the most common manifestation of lung disease in the neonatal period is respiratory distress syndrome, also related to surfactant dysfunction, and even pulmonary infections are recurrent.[12]

Here we provide a detailed description, focused on neuropsychiatric features, of a three-year old child and of her pedigree, in order to add complexity to the wide phenotypic variability of the disorder.

Patients Description and Methods

The child was a female born mildly preterm (34 weeks gestational age) by planned cesarean section due to intrauterine growth retardation. Birth weight was 1636 g (5th centile), length was 41 cm (5th centile) and head circumference was 30 cm (10th centile). Apgar score was 7 at fifth minute. Congenital hypothyroidism was detected at birth by neonatal laboratory screening, and a substituent therapy was started. Laryngomalacia was diagnosed at 3 months. The family history was positive for a non-progressive movement disorder. The mother presented with motor delay in childhood, successively evolved towards choreic movements and myoclonic jerks, involving also oro-facial muscles, with stuttering and mild dysarthria. Her brain Magnetic Resonance Imaging (MRI) was negative. She was affected by clinical hypothyroidism, needing the thyroid substituent therapy, and recently she started tetrabenazine therapy to control the movement disorder. She did not complete high school level education, and her adaptive functioning indicated a borderline cognitive impairment. The maternal grandmother presented a similar but less severe movement disorder associated with a partial thyroid agenesis that did not require replacement treatment (see Video 1).

The child was firstly admitted to our department at the age of 10 months for a motor delay, primarily characterized by postural immaturity, and followed up until the age of 40 months. Head control had been obtained at the age of 8 months, rolling at 12 months, without parachute reflexes in sitting position. Mild hypotonia and excessive motor activity, without a clear movement disorder, were detected. Spontaneous Babinski sign was present without signs of spasticity. Mild dysmorphic signs were noticed: prominent glabella, mild palpebral ptosis, bilateral inverse epicanthus, enlarged nasal bridge and nares, prominent columella, deep philtrum, wide mouth, thinned lips. At 16 months she was able to sit without support, but could not crawl. Ataxic features (sub-continuous postural rebalancing and imprecision in reaching objects) and hypotonia were observed. Cognitive performance was below the norm, with a developmental quotient between -2 Standard Deviations (SD) and -3SD, as assessed by Griffiths Mental Developmental Scales. Electroencephalogram and brain MRI were performed and resulted normal.

At the age of 28 months, crawling and wide-based gait with support were possible, characterized by instability and marked articular hyperextension. Gesture and pincer grasp were more precise. Mild hypotonia and laryngeal stridor were still present and tongue was maintained extruded. Play schemes were mainly sensomotor (See Video 2).

Thyroid appeared echographically hypoplastic, and substituent therapy, previously interrupted, was reintroduced because of mild elevation of Thyroid Stimulating Hormone blood levels.

Successively, at 40 months her neurological picture was still characterized by mild ataxic features, significantly improved with thyroid hormones therapy, while chorea was not present yet. Her cognitive level, evaluated with Bayley Scale of Infant and Toddler Development-III edition (Italian Standardization), was equivalent to a mental age of 19 months and 15 days (-3SD), configuring a moderate developmental delay. Her behaviour was characterized by motor instability and attention weakness, poor motivation and tendency to research preferred objects, which she used in a repetitive way.

Interaction was possible only for a short time and was greatly discontinuous. Speech was limited to sporadic vowels. Verbal comprehension was possible for simple and contextual messages, supported by gestures. She engaged relationships mainly with requisite aim. Pointing had not yet emerged and eye contact was poor. Response to name was highly inconsistent. Play schemes were limited to sensorial exploration and sporadic functional use of daily objects. She could participate in and anticipate social and play routines. Some imitation ability was present, but she did not have access to imaginary play. She was not yet able to choose between two alternatives. Sensorial interests and atypical attachment to objects she used stereotypically were noticed. At Autism Diagnostic Observation Schedule-2 Module 1 evaluation she met the criteria for a diagnosis of mild autism spectrum disorder.

Hearing evaluation had not detected any impairment.

Results

On the basis of the pedigree and the presence of movement disorder in the proband and her mother and grandmother, we indicated the molecular analysis focused on *NKX2-1* gene. A DNA change (cDNA): NM_003317 c.379delC Protein: p.R127AfsX7DNA change (hg19): g.36987220delC,

determining a novel frameshift mutation which predicted a truncated protein has been found in the three-generation members described. This mutation had never been reported in public databases.

In addition, array-CGH analysis, using a 60K array platform, detected an interstitial duplication of about 3.1 Mb in 22q11.2 ranging from 18,327,965 to 21,440,514 (GRCh37/hg19). Parental segregation analysis is ongoing.

Discussion

BHC, as suggested by its name, is a non-progressive movement disorder, usually not associated with cognitive impairment,[1,2] though cases with IQ reduced have been rarely described.[3,4]

To the best of our knowledge, autism spectrum disorder has not been reported to be related to BHC until now. The atypical BHC phenotype of our patient led us to deepen the diagnosis with the Array-CGH, as the first tier test in children with developmental delay/intellectual disability, autism spectrum disorders and dysmorphic features.[13] We detected the "22q11.2 duplication syndrome" (MIM#608363), a disorder with a highly variable expressivity and incomplete penetrance, that has been related to autism spectrum disorder[14] and ADHD.[15] Our patient met the criteria for both autism spectrum disorder and global developmental delay; moreover, her behavior was characterized by motor instability and attention weakness, though not meeting criteria for a diagnosis of ADHD.

The complex neurodevelopmental disorder affecting the proband could thus be concurrently provoked by a double genomic alteration, namely a chromosomal interstitial duplication and a genetic mutation, which mutually worsen the clinical picture. Thus, the co-occurrence of a dual diagnosis might further widen the BHC psychiatric correlations already reported.[4,6,8]

Considering the effects of *NKX2-1* on basal ganglia function,[11,16,17] its mutation might represent a double negative effect on neurodevelopment, being the subcortical structures crucially involved both in motor and non-motor higher functions such as cognition, attention, action finalisation and social behavior. Basal ganglia and cerebellar interconnections with different cortical areas of the brain, especially the prefrontal cortex, have recently been considered crucial for the processing and integration of different types of information. Anomalies of these circuits have been reported as related to some neurodevelopmental disorders.[16,17]

Basal ganglia regulate the balance between inhibition and excitation, thus modulating motor sequences and cognitive, relational, emotional and executive functions.[17]

As observed in other genetic conditions, environment, hormones, epigenetic factors and other modifying genes should be considered as contributors to the phenotypic heterogeneity in BHC.[18] In particular, thyroid hormones may mediate genomic actions involving the control of the expression of many genes involved in brain development and function of cerebellum, cerebral cortex and striatum.[19] Moreover, intrauterine growth retardation reported in our proband might be caused by both the maternal hypothyroidism[20] and the syndromic condition of the baby, and it might itself be a confounding factor for later cognitive/motor development.[21] We cannot exclude that 22q11.2 duplication might have contributed to hypothyroidism, hypotonia, language delay and mild dysmorphic features.[14]

As reported in other cases,[4,5] in our patient BHC was detected due to a motor delay associated with hypotonia. However, she had an unusual ataxic evolution rather than a choreic picture, though a similar picture has been already described.[22] Ataxia might be the onset of many movement disorders later evolving towards extrapyramidal involvement, and this finding could be explained considering the complex circuitry connecting basal ganglia, cerebellum and cerebral cortex.[16,17]

Early-onset ataxic pictures of unknown cause, following motor delay with normal imaging and associated with congenital or subclinical hypothyroidism and/or respiratory tract diseases, should thus raise suspicion of BHC and require mutation screening of the *NKX2-1* gene. Clinicians should consider BHC in differential diagnosis even in cases of intellectual and behavior impairment, especially if family history is strongly suggestive.

Variability in clinical expression among family members might be due to an incomplete penetrance of the disorder, a recurrent condition in autosomal dominant diseases, although correlations between genotype and phenotype have not been found in order to explain it[4,5]; moreover, it may represent subsequent evolutionary steps of the condition.

Conclusions

This report might contribute to a better understanding of BHC, that cannot be defined as a benign condition at least in some conditions. The occurrence of neurodevelopmental disorders such as global developmental delay/intellectual disability and autism spectrum disorder and of non-conventional motor signs such as ataxic features should not make clinicians exclude BHC, though this diagnosis might not be exhaustive and require further genetic studies. A two-hit model in which the concomitant presence of genomic alterations could influence clinical manifestations should always be evaluated. At the same time, as the clinical hypothyroidism can be detected following a silent period, a normal thyroid hormones dosage concomitant with the typical movement disorder should not make clinicians exclude BHC in the diagnostic process.

Informed Consent

Informed consent to execute genetic analysis and to publish Videos have been obtained by the patient's guardian.

Author Contribution

Declaration of Conflicting Interests

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Ethical Approval

Ethical Committee approved this study.

Supplemental Material

Supplemental material for this article is available online.

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