Journal of Child Neurology
25(4) 482-484

DOI: 10.1177/0883073809343315
http://jcn.sagepub.com

Early Testing for Huntington Disease in Children: Pros and Cons

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Abstract

We report 2 young children who are examples of the consequences of premature testing for Huntington disease. Premature testing of a child or fetus carries complex medical and psychological issues to both the child and the family that need to be considered and explored more than in an adult with Huntington disease. We suggest that a child at risk for juvenile Huntington disease not be tested until symptoms are progressive and consistent with the disease and all other mimickers are excluded. When testing is indicated, a multidisciplinary approach is essential to educate the family about the risks and benefits of testing and improve their coping skills when the final diagnosis is made.

Keywords

Huntington disease, juvenile Huntington disease, genetic testing

Received April 19, 2009. Accepted for publication June 25, 2009.

Huntington disease is a neurodegenerative disorder that leads to behavioral disturbances, movement disorder, and dementia. It is an autosomal dominant genetic disorder inherited through multiple generations with symptom onset in middle adulthood. The disease is caused by an expansion of polymorphic cytosine-adenine-guanine repeats in the Huntington disease gene, which encodes the huntingtin protein located on chromosome 4p16.3.[1]

Huntington disease phenotype varies depending on the age of onset. The most common onset is middle adulthood. Early-onset disease, prior to 21 years of age, occurs in 5% to 7% of patients and is called juvenile Huntington disease.[2] Two important factors that appear to be associated with early onset are the number of cytosine-adenine-guanine repeats and the sex of the parent.[3] In adult-onset disease, the number of cytosine-adenine-guanine repeats is usually 40 or more, while in juvenile form, the number is generally 60 or more. Juvenile Huntington disease is mostly paternally transmitted, but there have been a few documented cases where the mother transmits large enough nucleotide expansions to cause the early-onset disease in offspring.[4]

Although cognitive decline and behavioral disturbance are common to both the adult and juvenile forms, juvenile Huntington disease has a more varied symptomatology. Adults usually present with abnormal movements of the limbs and facial muscles, known as choreiform movements. However, the typical presentation of juvenile form is that of stiffness in the lower extremities, clumsiness, seizures, and swallowing and speech problems.[5] The symptoms progress over the years and render a child/young adult disabled and nonambulatory.[3] Because these symptoms are shared by other childhood neurological or psychiatric disorders, the initial diagnosis is often missed unless family history of Huntington disease raises suspicion. For example, early-onset disease may be mistaken for a developmental disorder, attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder, depression and/or anxiety, and epilepsy. A correct diagnosis is eventually arrived at as the disease progresses and the symptoms become increasingly severe.

Genetic testing for Huntington disease is available. It can be performed to diagnose a child with suspicious symptoms, to test the carrier status of a child who is asymptomatic, or prenatally to determine the carrier status of a fetus.[3] Such testing carries complex ethical issues and psychological and medical repercussions for the child and family that are much greater than for the adult. We present 2 children who were tested for Huntington disease and whose stories highlight the more negative than positive aspects of early childhood testing.

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Case Reports

Case 1

A 3-year-old developmentally delayed boy was referred to our institution because of refractory seizures. He started having seizures at 1 year of age, which were characterized by head drops, some of which led to injuries, and partial type seizures. Prior to our evaluation, he was treated with phenytoin, valproic acid, and levetiracetam without much success.

On physical examination, he was small, hypotonic, with weight and head size below the third percentile and length at the sixth percentile. On skin examination, he was found to have a couple of small depigmented spots and 1 large café au lait spot. Family history was strongly positive for Huntington disease, including his father and uncles, and the disease was traced back at least 4 generations. The main caregivers on the father's side (since his mother was not involved) requested genetic testing. The child was first tested at 2 years of age and the testing was positive for 86 cytosine-adenine-guanine (CAG) repeats. A diagnosis of early-onset Huntington disease was made and all signs and symptoms were attributed to the disease. Due to the refractory nature of his seizures and some skepticism regarding the symptomatic juvenile Huntington disease, further evaluation was conducted, including examination of the biological mother. She was found to have depigmented spots on the skin, adenoma sebaceum on the face, and limited cognitive function, all typical features of tuberous sclerosis. The mother, her sister, and the sister's 2 children have clinically confirmed tuberous sclerosis; thus, the child was not further genetically tested.

Additional studies included magnetic resonance imaging (MRI) of the brain, which showed small nodules in the subcortical white matter at the level of the gray–white junction scattered throughout both cerebral hemispheres and a larger left subependymal nodule attached to the right lateral ventricle (Figure 1).

An echocardiogram showed an echogenic mass in the left ventricle consistent with rhabdomyoma. A prolonged electroencephalogram (EEG)-video monitoring captured 2 seizure types: subtle head drops associated with an electrodecremental ictal EEG pattern and complex partial seizures with staring and lip smacking associated with right hemispheric spike-wave discharges. At the present time, he is on topiramate monotherapy with minimal improvement in seizure frequency. An epilepsy evaluation is being considered.

Case 2

A 4-year-old girl came to us for neurological evaluation after recent onset of abnormal arm and hand movements. The girl had been born full term to a 19-year-old woman who was tested during pregnancy for suspected Huntington disease and was found to be positive for 68 repeats of cytosine-adenine-guanine. Prenatal testing was done at the same time and the fetus was positive for a larger expansion of 80 cytosine-adenine-guanine (CAG) repeats, with no evidence of maternal contamination. The mother has had symptoms of depression and behavioral changes since the age of 16 years. At the time of evaluation, the child was neurodevelopmentally at age-appropriate level, and on both general and neurological examination, she was normal. During the examination and while excited, she exhibited typical movements of arm flexion at the elbows and hands at the wrists. Movements were diagnosed as benign stereotypy.

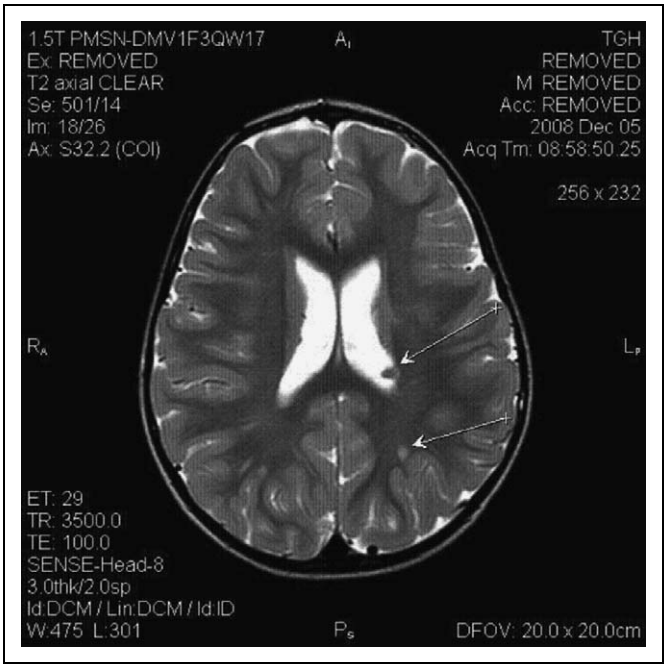

Figure 1. Magnetic resonance imaging (MRI) of the brain, T2 axial image. Subependymal nodule attached to the right lateral ventricle and 1 in the subcortical region on the right (arrows).

Discussion

We report 2 young children with consequences of premature testing for Huntington disease. In the first case, the presence of hypotonia, seizure, and developmental delay were incorrectly attributed to juvenile Huntington disease. Although seizures are a common symptom of juvenile-onset Huntington disease, affecting 25% of children, their presence does not necessarily mean that they are directly related to it.[3] Our patient had treatment-resistant seizures for over a year before a diagnosis of tuberous sclerosis was made. Fortunately, there was no delay in treatment of his seizures, but the treatment was not directed toward the multiple seizure types he has had. Currently, there are no treatment guidelines for juvenile Huntington disease, and only symptomatic treatment is provided with medications, not approved by the US Food and Drug Administration for children. Early diagnosis and detection of symptoms will not provide a cure and, more importantly, will not affect the prognosis. Our patient with treatment-resistant seizures and a delayed diagnosis of tuberous sclerosis was, in addition, labeled with a terminal Huntington disease. The

child's father who is now exhibiting typical signs of the disease must deal not only with his problems but also carry the guilt of having passed on the disease to his child. It is well known that psychiatric symptoms, especially depression with completed suicide, are elevated in patients with Huntington disease.[6] The anxiety and depression are likely to be compounded if one knows his own child has inherited the disease.

The second case demonstrates the risk of predictive testing in a child and also is an example of the uncommon large cytosine-adenine-guanine (CAG) expansion transmitted from mother to her child. The 4-year-old girl was evaluated because of suspicion of having early manifestations of juvenile Huntington disease. In turn, a diagnosis of benign stereotypic movements was made. Although this diagnosis was reassuring, the child's main caregiver, her maternal grandmother, still is gripped by the positive fetal test. Her life has forever changed as it revolves around this child and her own daughter with this dreadful disease. She has become more protective of both and overindulgent. She lives in anticipation of new symptoms and she feels she cannot waste any time. Despite the diagnosis stigmatizing her granddaughter, the grandmother does not regret the prenatal testing. She feels she needs to know what the future holds to help her prepare for the road ahead. Nevertheless, the argument can be made that the strain and pressure this woman feels is unnecessary.

Conclusion

Genetic testing is a specific tool that aids in the early diagnosis of Huntington disease when such is clinically suspected. However, the risks of predictive genetic testing in children need to be carefully examined as they may outweigh the benefits in some cases. The positive results both prenatally and in a young child can cloud the clinical picture, creating a catchall explanation for medical and behavioral problems of the child, and lead to misdiagnosis and delay in proper treatment.[5]

Genetic testing for early onset of the disease brings up a number of issues that are uncommon to the adult. Unlike an adult facing genetic testing, the child cannot consent to the testing and he or she lacks mature coping strategies. Adult guidelines are very straightforward and comprehensive, involving the individual and family who choose to be tested for the disease and recommend extensive psychological counseling.[7] There are no set guidelines for genetic testing in children and, more importantly, no cure or specific treatment for the disease. Testing positive for the Huntington disease mutation does not necessarily imply that the child's current or future clinical symptoms are disease related. The child is now given a dismal prognosis without the benefit of effective treatment or consideration of a different diagnosis for which treatment may be available. The entire family's structure and relationships may change as some will experience survivor guilt as the life cycle has been altered and the emotional burden of being the caretaker escalates. In addition, social stigma, as well as employment and insurance discrimination, may affect the child as he or she grows older.[5]

We suggest that a child at risk for Huntington disease not be tested until symptoms are progressive and consistent with the disease and all other mimickers are excluded. To that end, the child will need frequent and regular visits with a pediatric neurologist and/or child psychiatrist who will monitor the child's development, behavior, and neuropsychiatric status and guide the family regarding genetic testing. In addition, we strongly recommend that a geneticist or genetic counselor be involved in the care of these patients to provide counseling to the families about the intricate aspects of genetic testing. This thorough multidisciplinary approach may help avoid the premature psychological burden of a misdiagnosis on the family and improve the child's coping skills when the final diagnosis is made.

Acknowledgments

The authors thank Marcia A. McCall, AB, MTS, for coordinating neurology visits for children and their families and providing psychological support to them; Juan Sanchez-Ramos, MD, for his referral of the children; and Emily Van Orden, BA, for assisting in the preparation of this manuscript.

Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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