Deciphering the Complexities of Rett Syndrome

Rett syndrome is a neurodevelopmental disorder that is seen most often in girls, with an incidence of 1 in 10,000-22,000 live female births. The prevalence among males is not known, because the severity of infantile encephalopathy, early death, or lack of classic symptoms—even in the few older boys that survive—preclude precise identification, except when there is familial occurrence.

In 1999, researchers identified the genetic cause for Rett syndrome: mutations in the MECP2 or methyl cytosine-binding protein 2 gene, which is located at chromosome Xq28. MECP2 mutations have been confirmed to be present in some cases of childhood schizophrenia, classic autism, and learning disabilities. Nevertheless, most cases of Rett syndrome are random, with fewer than 1% of recorded cases being identified as inherited.

The Rett-linked disorder was first recognized in 1986 by the late Viennese physician Dr. Andreas Rett, who observed two girls in his waiting room with the same stereotypic hand-washing motion.

Today, a sequence of clinical features—including decelerating head growth and the loss of hand use, speech, and communication—is recognized, starting in the second half of the first year of life and following a period of apparently normal development.

Subsequent features include poor eye contact, which may be mistaken for autism; stereotypic behaviors, such as hand-wringing or hair-pulling; and respiratory irregularities, such as hyperventilation, breath-holding, or apnea. EEG spikes in the central parietal regions are visible early, with or without seizures. After the first decade of life, there is considerable clinical stabilization, with amelioration of seizures and respiratory irregularities.

However, there is also progressive rigidity of limbs and scoliosis. Life expectancy varies, with early death more common in males. Death from sudden unexpected events occurs in females in the first two decades of life through adulthood.

The course of Rett syndrome varies considerably from child to child. The impact on families, however, is universally devastating, as they experience their child’s developmental delay, neurologic abnormalities, and the uncertainty of how the disorder will fully manifest in their child.

Some anxiety can be alleviated if the pediatrician dispels parents’ fears that Rett syndrome is a neurodegenerative disease. Patients with Rett syndrome show abnormal neuronal morphology, but not increased neuronal death. They do not progressively deteriorate, as with Tay-Sachs disease; rather, their course stabilizes with age.

Parents also can be spared some anxiety caused by the use of the present four-poster staging system, which conveys a sense of progressive clinical deterioration to them. Presently, the broad phenotype of Rett syndrome is more widely recognized, and is confirmed by mutation analysis.

Parents also should understand that Rett syndrome is not an autism spectrum disorder, as has been suggested; many affected children can maintain eye contact and communication skills.

The most important consideration for the pediatrician is to conduct regular head-circumference measurements, and to retain a high index of suspicion if they encounter a young infant, particularly a female, who is more hypotonic than usual and whose velocity of head growth is not in keeping with his or her age.

Without careful monitoring, a head circumference at the 40th percentile at 4 months could be mistaken as normal, despite the child’s slipping from the 50th percentile at birth and 2 months.

Children with MECP2 mutations do not have changes in the white matter on MRI; this characteristic may be useful to distinguish Rett from other neurologic diseases.

It is not known why some cases are more severe than others, but scientists are studying genotype-phenotype relationships in Rett syndrome. Scientists have demonstrated that the mutations p.R131C and p.R294X have a less severe phenotype, whereas the p.R207X mutation is associated with higher severity (Neurology 2008;70:868-75).

Significant differences by mutation have been seen for individual phenotypic characteristics such as ambulation, hand use, and language (Neurology 2007;70:1311-7).

Further improvements in the identification of correlates between specific mutations and clinical or biochemical markers will allow physicians to better counsel parents on their children’s clinical profiles.

There is no cure for Rett syndrome. Treatment is focused on the management of symptoms using a multidisciplinary approach. Medications can control seizures and improve behaviors; hydrotherapy and occupational and speech therapy are essential to maintain neuromotor activity. Efforts are being made to modify the clinical course of the disorder.

Thyroid Dysfunction Is Linked to Pediatric Headache

Thyroid disease might play a role in the etiology of pediatric headache.

The findings of a new study conducted at the Cleveland Clinic revealed statistically significant associations between hyper- and hypothyroidism and headaches, which, if confirmed, could have an impact on the diagnosis and management of pediatric headache, according to investigators.

Although thyroid dysfunction has been linked to headache in adults, the presence of such a link has been unexplored in the pediatric population, medical student Ms. Stanga, along with Dr. Douglas Rogers, head of the Cleveland Clinic’s pediatric endocrinology section, and Dr. A. David Rothner, director of the clinic’s pediatric/adolescent headache program, conducted a retrospective study of children and adolescents being treated for hypo- or hyperthyroidism in the hospital’s pediatric endocrinology department.

The investigators reviewed the charts of 275 patients aged between 5 and 18 years who were seen in the endocrinology clinic between Jan. 1, 2006, and Dec. 31, 2006, and collected data regarding age, sex, thyroid dysfunction, headache presence, and etiology.

Patients with congenital hypothyroidism and those with incomplete records were excluded from the analysis. Of the 275 patients, 248 met the study criteria and were included in the analytical sample. Ms. Stanga noted.

Both hyperthyroidism and hypothyroidism were associated with headache in the study population to a statistically significant degree, said Ms. Stanga.

Specifically, 36.2% of hypertensive patients and 18.5% of hypothyroid patients experienced headache, she observed.

Correlations between hyperthyroidism and new daily persistent headache as well as between hypothyroidism and chronic migraine were observed.

Given these findings, a prospective study is warranted to further quantify the occurrence of headache and its particular characteristics in this population, Ms. Stanga commented.

The medical student added that “an attempt should also be made to determine whether headache frequency changes in response to the treatment of thyroid disease.”

If further studies confirm the significant association between thyroid dysfunction and headache, the inclusion of thyroid work-up might be considered part of a standard evaluation for headache in this patient population, according to Ms. Stanga.