Study examines challenges of diagnosing neurofibromatosis type 1-like syndrome

November 17 2009

An analysis of patients with a syndrome similar to the genetic disorder, neurofibromatosis type 1, indicates that diagnosis may be difficult because of shared clinical findings, such as certain pigmentary characteristics, according to a study in the November 18 issue of *JAMA*.

Neurofibromatosis type 1 (NF1), an autosomal dominant disorder affecting approximately 1 in 3,000 individuals worldwide, is characterized by multiple café au lait macules (CALMs; small areas of discoloration of the skin [light-brown]), skin-fold freckling and tumors of the nervous system. Other frequently observed features are certain bone abnormalities, short stature, macrocephaly (an abnormally large head) and learning problems, according to background information in the article. NF1 diagnostic criteria were established by the National Institutes of Health (NIH) and are widely used to make the diagnosis using information obtained from physical examination, family history, and radiologic studies. A genetically distinct but similar disorder, caused by mutations of the gene SPRED1 was recently identified (and recently named Legius syndrome). The authors write that this disorder, characterized mainly with CALMs, axillary freckling and macrocephaly, may be underestimated.

Ludwine Messiaen, Ph.D., of the University of Alabama at Birmingham, and colleagues conducted a study to determine the frequency, mutational spectrum, and phenotype of neurofibromatosis type 1-like syndrome (NFLS; Legius syndrome). The study included 23 unrelated probands (first affected family member who seeks medical attention for a genetic

disorder) carrying a SPRED1 mutation identified through clinical testing, who participated with their families in a genotype-phenotype study (2007-2008). In a second cross-sectional study, 1,318 unrelated anonymous blood samples collected in 2003-2007 from patients with a broad range of signs typically found in NF1 but no detectable NF1 germline mutation underwent SPRED1 mutation analysis.

The researchers found that among 42 SPRED1-positive individuals from the clinical cohort, 20 (48 percent) fulfilled NIH NF1 diagnostic criteria based on the presence of more than 5 CALMs with or without freckling or an NF1-compatible family history. "None of the 42 SPRED1-positive individuals had discrete cutaneous or plexiform neurofibromas, typical NF1 osseous [composed of or containing bone] lesions, or symptomatic optic pathway gliomas [brain tumors]," the researchers write.

"In the anonymous cohort of 1,318 individuals, 34 different SPRED1 mutations in 43 probands were identified: 27 pathogenic mutations in 34 probands and 7 probable nonpathogenic missense mutations in 9 probands. Of 94 probands with familial CALMs with or without freckling and no other NF1 features, 69 (73 percent) had an NF1 mutation and 18 (19 percent) had a pathogenic SPRED1 mutation. In the anonymous cohort, 1.9 percent of individuals with the clinical diagnosis of NF1 according to the NIH criteria had NFLS."

"The dermatologic phenotype in young children with a SPRED1 mutation could not be differentiated from NF1 and nearly half of individuals (20/42) with a SPRED1 mutation fulfilled the NF1 diagnostic criteria based on presence of more than 5 CALMs with or without skinfold freckling and with or without familial history," they write.

The authors add that although an NF1 diagnosis may become apparent with the passage of time, the diagnosis will remain uncertain for

individuals who do not develop other signs of NF1, and that molecular genetic testing can resolve the diagnosis in most such cases. "In case of diagnostic uncertainty, we recommend that NF1 should be analyzed first and, if negative, SPRED1 testing should be considered in patients with CALMs with or without freckling and no other NF1 diagnostic features. Identification of a SPRED1 mutation may relieve a psychological burden from families who otherwise would be in a waiting mode for potential serious NF1-associated manifestations."

"… it is important that clinicians, including general practitioners, clinical geneticists, pediatricians, ophthalmologists, dermatologists, neurologists, and oncologists, who are involved in the care, diagnosis, and treatment of individuals with NF1, should be aware that Legius syndrome can resemble NF1."

More information: *JAMA*. 2009;302[19]:2111-2118.

Source: JAMA and Archives Journals (news : web)