Fragile X syndrome: Are paediatric health care providers missing the diagnosis?

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A 12-month-old boy is referred to you for developmental delay. He was slow to roll over and began sitting unassisted at 10 months of age. In retrospect, the parents believe he was floppy and less sociable compared with his older sister. Otherwise, his health is generally good, with normal growth. The pregnancy and delivery were uncomplicated. On the maternal side, an aunt experienced infertility secondary to early menopause in her twenties, and the grandfather, currently in his sixties, has experienced some balance problems and a tremor.

On physical examination, the height, weight and head circumference are all in the 50th to 85th percentiles. There are no dysmorphic features. The examination is noteworthy for generalized low muscle tone and reduced social interaction. The child is diagnosed with global developmental delay. Investigations show a full mutation in the *FMR1* gene, consistent with fragile X syndrome (FXS). A referral for genetic counselling is recommended.

LEARNING POINTS

- Prevalence of FXS has been estimated to be one in 5000 newborn males in the United States (1). Many Canadian paediatricians have never encountered a patient with FXS, leading some to question whether there are ethnic or geographical variations (2).
- FXS is an X-linked condition that results from expansion of a CGG repeat sequence in the *FMR1* gene. Normally, there are fewer than 55 repeats, but in FXS there are more than 200 repeats, which is termed a full mutation. The presence of 55 to 200 repeats is termed a premutation; these premutations are unstable and can undergo further expansion on transmission from mother to child. Males with the premutation, in contrast, will always pass on only the premutation to all of their daughters, but none of their sons (3).
- Males with FXS typically present with global developmental delay in infancy, and ultimately have moderate to severe intellectual disability. Concomitant extreme social anxiety is common, as is attention deficit hyperactivity disorder (ADHD), and many affected individuals will also receive a diagnosis of autism. Significant behavioural issues are common. Associated medical complications may include gastro-esophageal reflux, seizures, recurrent otitis media, strabismus, joint laxity and mitral valve prolapse (3). Physical features of FXS, such as a long face and prominent ears, develop with age, and infants do not have a recognizable phenotype. Macro-orchidism is not apparent until after puberty.
- Females with a full mutation may fall anywhere on a spectrum from healthy with above average intellectual ability to learning disabilities or severe intellectual disability, and any of the associated features of FXS (3).
- The premutation, present in up to 1.7% of women (4), is more common than the full mutation. There is an associated 20% risk for primary ovarian insufficiency and infertility (5). Men with the premutation older than 50 years of age are at increased risk of developing a tremor-ataxia syndrome (6). The possibility that the premutation may also cause neurodevelopmental problems, including developmental delay, autism, ADHD and anxiety disorders, is currently under investigation (7,8).
- Management of FXS should include early developmental intervention with behavioural therapy and speech therapy. Medication may be indicated to treat symptoms of ADHD, anxiety or aggression. Although there are limited data to provide evidence-based approaches to therapy, there are expert opinion-based consensus guidelines available through the Fragile X Clinical and Research Consortium at www.fxcrc.org. A multidisciplinary approach to care is most effective and, where possible, assessment by a developmental paediatrician, clinical geneticist or other specialist with expertise in FXS is recommended (3). Clinical trials of pharmaceutical therapies that address the underlying molecular pathophysiology are in progress and may lead to a targeted treatment option in the future.
- Any child, male or female, presenting with developmental delay should be tested for FXS. The diagnostic yield in this unselected population is approximately 1% to 3% (9). An early diagnosis can lead to earlier intervention and supports.
- Confirmation of FXS in a child is also important because it enables accurate genetic counselling for parents on the risk of having another affected child. Prenatal diagnosis would become an option for them in a future pregnancy. Genetic testing of family members can also identify others with the premutation. Counselling young women with the premutation on the risks of having a child with FXS or having infertility can help with their family planning (10). Thus, genetic testing for the *FMR1* premutation should be offered to any woman with a maternal family history of unexplained intellectual disability (11).
- The Canadian Paediatric Surveillance Program study of FXS was launched in April 2012 to ascertain the population prevalence, along with regional/ethnic variation and the burden of illness. The study will increase paediatricians' awareness of the possibility of FXS when assessing children with developmental delay. In the first eight months of surveillance, 11 cases have been reported.

The Canadian Paediatric Surveillance Program (CPSP) is a joint project of the Canadian Paediatric Society and the Public Health Agency of Canada, which undertakes the surveillance of rare diseases and conditions in children and youth. For more information, visit our website at www.cpsp.cps.ca.

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