

Should healthy children be tested for genetic disease predisposition?

Predictive testing should be in the child's best interests

Imagine the following scenario: A six year old girl is diagnosed with thrombocytopenia after an unusually severe nosebleed. As a newborn she had anaemia and hyperbilirubinemia, and an exchange transfusion was considered. Her three year old sister had transient mild thrombocytopenia in conjunction with a respiratory tract infection; the girls and their younger brother are generally healthy. Both parents are in good health. The mother is 15 weeks pregnant. The parents found the article on *ADAMTS13*-associated congenital thrombotic thrombocytopenic purpura (TTP) by Anne Sophie von Krogh et al. (1) in this issue of the Journal of the Norwegian Medical Association and ask: Could our daughters have this rare disorder? Should our son be tested for it? And what about our new baby when s/he is born?

The anaemia and increased bleeding tendency in *ADAMTS13*-associated congenital TTP may present at different phases in life and may vary greatly in severity, even within the same family. Prophylactic treatment can prevent organ damage and, in a worst case scenario, premature death (1). The disorder is a rare cause of thrombocytopenia – but collectively rare genetic diseases are common. McCandless and colleagues, for example, found an underlying genetic diagnosis in approximately one in three admissions to a large children's hospital in the USA (2).

The Norwegian law which regulates use of biotechnology in human medicine (the Biotechnology Act) (3), defines genetic testing as «... all types of analyses of human genetic material, both at the nucleic acid and chromosomal level, of gene products and their functions, or the examination of organs, for the purpose of obtaining information about inherited human traits».

The girls' presentations are consistent with *ADAMTS13*-associated congenital TTP. Genetic testing of them is therefore *diagnostic* and can be requested by their physician. The asymptomatic brother and the new baby, however, raise the issue of *predictive* testing. Testing of healthy children for genetic predisposition to disease – predictive testing – is regulated by the Biotechnology Act as well and requires genetic counselling. Such testing «... shall not be performed on children under the age of 16 years unless the testing can identify circumstances in which treatment may prevent or reduce damage to the child's health.»

The combination of new tests, increasingly sophisticated bioinformatics and increasing international collaboration means that far more individuals with rare diseases now receive a causal diagnosis (4). Treatment is still most often symptomatic but there are important exceptions: we know, for example, of roughly ninety rare congenital metabolic disorders that affect the brain, in which targeting the pathophysiological process may modify the disease course, lead to more precisely tailored symptomatic treatment or even prevent intellectual disability (5). Fölling's disease, or phenylketonuria, is the prototype of such a disease.

Predictive testing is indicated when the results affect the child's medical management including medical treatment, or the initiation or termination of follow-up. For serious and potentially treatable disorders that may present at a young age, it makes sense to test the child early. For disorders that may present in the neonatal period,

such as *ADAMTS13*-associated congenital TTP, a plan for testing can be agreed upon before the child is born. For diseases that present later in childhood, the best time for testing can be discussed with the parents. The child can be included in the discussion if s/he is mature enough (6).

Diagnosis specific monitoring of healthy children is indicated for conditions such as neurofibromatosis type 2, a syndrome that predisposes to central nervous system tumours. When a parent has neurofibromatosis type 2, each of his/her children has up to a 50% probability of inheriting the causative pathogenic gene variant. Testing of healthy children can spare parents for unnecessary anxiety about this serious disease and should be done before age 10–12 years when multi-specialist follow-up should start (7).

What about the family described earlier? If the girls have *ADAMTS13*-associated congenital TTP, the parents should be offered genetic counselling at one of the country's departments of Medical Genetics. Their son and the new baby can be tested predictively because the result may have therapeutic implications in childhood, as described in the current review (1). Testing is quick, inexpensive and reliable when the family's mutation is known. In autosomal recessive disorders, increased risk of developing the condition – 25% at birth – is most often limited to siblings of an affected individual. The main purpose of genetic counselling in this situation is to emphasise for the parents that they could receive the result they do *not* want – that one or both of their other two children have an increased risk of developing *ADAMTS13*-associated TTP. If there are other couples in the family where both parents are related to the affected child, they too may be at increased risk of having children with the disorder and should be offered genetic counselling.

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