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LETTER TO THE EDITOR *Women with bleeding disorders*

An uncommon case of a female carrier of two distinct X-linked disorders

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Prenatal diagnosis (PD) performed on chorionic villus biopsy or amniotic fluid provides a diagnosis for genetic disorders, such as haemophilia A (HA) and Charcot-Marie tooth disease (CMT), in the first trimester of pregnancy. Recessive X-linked diseases are a group of disorders almost exclusively affecting male patients, while carrier females are usually asymptomatic: e.g. mutations in the factor VIII gene (F8), resulting in a deficient or defective coagulation FVIII, cause the bleeding tendency known as HA [1].

Charcot-Marie tooth disease, the most common degenerative disorder of the peripheral nervous system, is a clinically and genetically heterogeneous group of inherited neuropathies [2]. The classification is based on the type of the neuropathy (axonal or demyelinating) and on the mode of inheritance, i.e. autosomal dominant, autosomal recessive or X-linked. While electrophysiological tests suffice to determine the type of neuropathy, genetic heterogeneity requires accurate series of molecular tests to identify the gene that is involved in the disorder [3]. CMT1X is the most common X-linked form of CMT disease [4]. The clinical phenotype is characterized by progressive distal muscle atrophy and weakness, areflexia, and variable sensory abnormalities. Affected males have moderate-to-severe symptoms, whereas heterozygous females are usually mildly affected or even asymptomatic.

The presence of two distinct genetic, segregating X-linked disorder within the same family has rarely been reported. We describe an asymptomatic female, belonging to a sporadic haemophilia A family who was referred to our Laboratory for genetic counselling.

Pedigree analysis revealed that: (i) her brother was the only member of the family affected by severe HA; and (ii) since the age of 10 years, her father had shown clinical symptoms of leg muscles weakness and 'pes cavus'. On the basis of these clinical data, CMT disease was hypothesized in the father. The first molecular studies on the father's DNA, ruled out a duplication of the peripheral myelin protein 22 (the most common molecular defect in CMT) and any mutation in this gene as well as in the myelin protein 0 gene. Sequence analysis of the whole Gap-junction protein beta-1 (GJB1) gene, located on the X-chromosome (Xq13.1), revealed a guanosine to adenosine change at nucleotide 491 in exon 2. It provoked an arginine to glutamine substitution (codon 164), which is already described in the CMT mutations database (http://www.molgen.ua.ac.be/CMTMutations).

With regards to HA disease, the entire coding region of the F8 (chromosome Xq28), including the splice sites, was screened in the haemophiliac patient. A thymidine to cytosine mutation was identified in exon 16, resulting in a phenylalanine to serine substitution (codon 1785) [5]. The proposita's DNA was amplified for both mutations. She was found to be an asymptomatic double carrier of two unrelated X-linked disorders showing a paternal abnormal CMT gene and a maternal defective F8. The study was performed after informed consent of all members was obtained.

To our knowledge, this is the first report of a co-inheritance of these two distinct X-linked disorders. Crossing-over events between CMT and HA genes may occur with high frequency both due to their distance on the X-chromosome and to the absence of linkage disequilibrium between these loci. Based on these data, it appears mandatory to perform genetic counselling early before this patient's

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pregnancy to carefully clarify that in her male progeny, 75% of all sons will be affected (50% by one of the two disorders and 25% by both) and 25% of the sons will be healthy. In the female progeny, 50% of the daughters will be carrier of one of the two diseases, 25% will be carriers of both disease and 25% will result in a non-carrier status.

It is important to keep in mind that despite the improvement in the quality of life of HA patients, in our country most carriers request PD, and the majority decide to abort affected male foetuses. Moreover, genetic counselling for CMT is rather difficult as it is a heterogeneous disorder: clinical phenotypes are quite different and severity of symptoms may vary greatly; a child may be more severely disabled than his parent or vice versa. Therefore, a PD could be offered to this woman and the molecular research on foetus DNA must be performed for both the mutations.

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Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

References

1 Castaldo G, D'Argenio V, Nardiello P *et al.* Haemophilia A: molecular insights. *Clin Chem Lab Med* 2007; **45**: 450–61.
2 Züchner S, Vance JM. Mechanisms of disease: a molecular genetic update on hereditary axonal neuropathies. *Nat Clin Pract Neurol* 2006; **2**: 45–53.
3 Chance PF. Genetic evaluation of inherited motor/sensory neuropathy. *Suppl Clin Neurophysiol* 2004; **57**: 228–42.
4 Rouger H, LeGuern E, Birouk N *et al.* Charcot-Marie-Tooth disease with intermediate motor nerve conduction velocities: characterization of 14 Cx32 mutations in 35 families. *Hum Mutat* 1997; **10**: 443–52.
5 Bicocchi MP, Pasino M, Lanza T *et al.* Analysis of 18 novel mutations in the factor VIII gene. *Br J Haematol* 2003; **122**: 810–7.