



A rare case of co-existence of hereditary multiple exostoses and steroid-sensitive nephrotic syndrome

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Abstract

Introduction. Hereditary multiple exostoses (HME) is a rare autosomal dominant disorder, caused primarily by loss of function mutations in 2 genes *EXT1* and *EXT2* linked to the synthesis of heparan sulfate (HS). Deficiency of HS causes the formation of numerous benign cartilage-capped bone tumours. There is no causal treatment for this disease. Surgery is recommended only for symptomatic lesions and malignant transformations.

Case Report. The case is presented of an 11-year-old boy with a pathogenic variant in the *EXT1* gene and steroid-sensitive nephrotic syndrome (NS), diagnosed at the age of 8. There are only single reports of the co-existence of HME and NS. Conceivably, HS deficiency may explain ultra-structural changes in kidney glomeruli that result in NS, although unknown, second-hit risk factors seem to have significant contributions. Further research is necessary.

Key words

nephrotic syndrome, genetic disorders, Hereditary multiple exostoses, *EXT1* gene

INTRODUCTION

Hereditary multiple exostoses (HME) (OMIM: 133700 and 133701), also called hereditary multiple osteochondromas, is a rare autosomal dominant disease with a prevalence of 1:50.000 in Western countries [1]. It is linked to loss of function mutations in two genes, *EXT1* (OMIM: 608177) on chromosome 8 and *EXT2* (OMIM: 608210) on chromosome 11, which are detected in 70–94% of affected patients with predominance of the *EXT1* gene [2]. The main symptom of HME is the formation of exostoses in metadiaphyseal segments of bones modelling the adjacent tissues, nerves, and vessels. Affected bones are deformed and prone to damage [3]. Usually, the diagnosis is made before the age of 12. Deformations and chronic inflammation influence the patient's quality of life, especially since around 60% of children and 80% of adults with HME experience chronic pain [3]. At present, the treatment of HME is symptomatic and limited to pain management. Surgical removal of exostoses is approved only in suspected malignancy, the occurrence of severe pain, and spine intracanal growths.

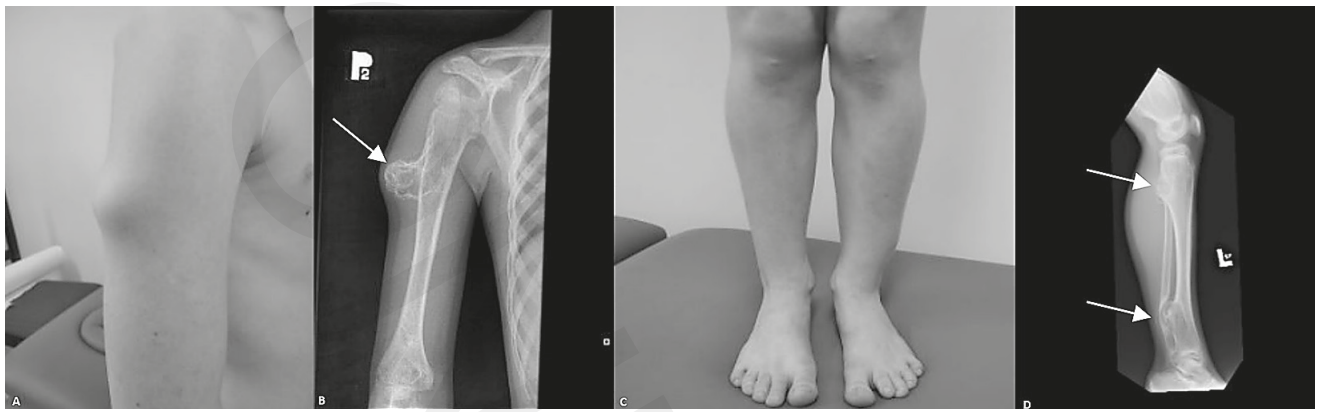
The case is presented a case of an 11-year-old boy with HME and steroid-sensitive nephrotic syndrome (NS). To date, only single cases of the co-existence of this disease have been reported. As HS is a compound of the glomerular basement membrane (GBM), mutations of *EXT1* and *EXT2* genes may be potentially involved in glomerular injury, leading to kidney ultrastructural changes resulting in the NS [4].

CASE STUDY

A boy of Polish descent, the 4th child of non-consanguineous parents, was born at the 38th week of gestation by Caesarean section due to detachment of the placenta. Pregnancy was uneventful. Body weight and length at birth – 3,970 g (75th percentile), and 59 cm (99th percentile), respectively. Apgar scores were 10 at the 1st and 5th minutes. The first small lesions occurred bilaterally and asymmetrically on fingers in early infancy, which at school-age resulted in handwriting difficulties. Due to the slow growth, most of them were initially visible only in imaging studies. At the age of six, there were four palpable tumours in the left lateral malleolus, bones of the right upper limb, and scapula. The boy underwent a knee injury complicated by the fracture of one of the osteochondromas, resulting in chronic kneeling and crouching problems. Over the next five years, three new, palpable lesions appeared in the left femoral, tibial, and fibular bones.

At the age of eight, the boy was admitted for the first time to the Department for Paediatric Nephrology. He presented with massive, generalized oedema, ascites, and pleural effusion. Based on laboratory findings (Tab. 1), NS was diagnosed and standard treatment with prednisone at a daily dose of 60 mg/m² was introduced. The proteinuria subsided on the 8th day of therapy and steroid-sensitive NS was diagnosed.

The family history included multiple osteochondromas in the patient's father and siblings, thrombophilia in the father and one of the patient's sisters, and NS in two of the grandfather's cousins from his father's side. However, due to deaths of the cousins, more accurate data could not be obtained. Because of the concern for the possibility of thrombophilia the boy was consulted with a paediatric



A. Right arm of the presented patient at the age of 11. Note tumor caused by osteochondroma (arrow). **B.** The same osteochondroma in the X-ray in the AP position – arrow (Department of Pediatric Radiology, Medical University of Lublin). **C.** Legs of the presented patient. Note the crooked left leg due to the tumor growth (arrow). **D.** X-ray of the left lower limb of the presented patient in the lateral position, note multiple osteochondromas - arrows (Department of Pediatric Radiology, Medical University of Lublin)

Table 1. Laboratory results of the patient at the onset of nephrotic syndrome at the age of 8

Laboratory parameters	Reference Range	Patients result
Urine		
Protein	0	+3
Urine sample protein, mg/dl	0–15	5945,7
24-hour urine protein test, mg/24h	0–140	8369,10
Blood		
Albumin, g/dl	3,8–5,4	1,75
Total cholesterol, mg/dl	115–190	376
Triglycerides mg/dl	≤ 150	212
Creatinine, mg/dl	0,4–0,6	0,38
Urea, mg/dl	15–36	56,6
Free protein S, %	74,1–146,1	61,9
Protein C, %	70–140	187
Factor V Leiden	2,4–3,32	2,54
Calcium, mmol/l	2,2–2,7	1,90
Total protein, g/dl	6–8	3,65
Fibrinogen g/l	2–4	7,33

haematologist, and later with a clinical geneticist. With NS, exostoses and possible thrombophilia genetic evaluation was performed (whole exome sequencing WES) and revealed a pathogenic variant in *EXT1* gene (NM_000127.3(*EXT1*):c.1056+1G>T). Consequently, the patient was diagnosed with HME. Within a three years follow-up, the patient had three more relapses of NS, following respiratory tract infections. Currently, at the age of 11, the patient has been in NS remission for 10 months and the last corticosteroid treatment was completed six months ago. His current height is 145 cm (51st percentile). Multiple osteochondromas cause pain and movement limitations (Fig. 1). Surgical removal of exostosis on the left tibia is under consideration due to deformation and movement restriction in the left lower limb.

DISCUSSION

The etiology of most cases of steroid-sensitive NS remains unknown. Advances in genetics in the last two decades have revealed over 50 single-gene causes and genetic risk loci for

steroid-resistant NS. On the contrary, the genetic architecture of steroid-sensitive NS is only poorly understood. Recent studies suggest the role of MHC class II molecules, such as HLA-DQA1 and HLA-DQB1, as risk factors for steroid-sensitive NS. However, an unknown second hit risk loci outside of the MHC locus and environmental factors seem to make crucial contributions to the disease. Outside HLA, some variants of the *NPHS1* gene responsible for the congenital nephrotic syndrome of the Finnish type are associated with susceptibility to steroid-sensitive NS [5]. Furthermore, Watts discovery of nephrin autoantibodies in patients with minimal change disease provides support for autoimmune etiology [6], which explains why acute infections and insect stings are well-known triggers for the onset and relapse of NS [5]

EXT1 and *EXT2* genes are responsible for the production of exostosins 1 and 2 involved in the synthesis of heparan sulfate (HS), present in the glomerular basement membrane (GBM). Normal GBM is rich in HS proteoglycans, providing a negative charge barrier to macromolecules. It is well documented that loss of this ionicity causes proteinuria and results in increased GBM permeability. Products of both the *EXT1* and *EXT2* genes form a Golgi reticulum-based complex that is essential for the activity and production of glycosyltransferase enzyme, which is responsible for the chain polymerization of HS [3]. In the presented case, the mutation affected a donor splice site in intron 2 of the *EXT1* gene resulting in disruption of RNA splicing leading to the loss of protein function. Although relationship to bone formation is quite well established, the connection with NS remains unclear. The fact that mutations in the *EXT1* and *EXT2* genes can lead to NS was first reported in 2008 by Roberts and Gleadle [4] who described a 37-old-woman with an *EXT1* gene mutation and steroid-sensitive NS. Interestingly, a recent study in Denmark with a group of 19 HME patients showed no GBM and glycocalyx changes that could be responsible for NS in patients with HME and a mutation in a single allele of the *EXT1* and *EXT2* genes. However, one patient in that study had an unexplained kidney failure, and histopathological changes matched those described by Roberts [7]. Both authors agree that mutation in a single allele is insufficient to cause such abnormalities and there must be an additional triggering factor leading to the observed phenotype [4,7]. Cases of NS in the patient's family make this theory plausible, although what additional predisposing factors must occur requires further studies.

Moreover, Chen et al. knocked out podocyte-specific *EXT1* on mice which resulted in the development of morphologic features similar to minimal change disease in humans. However, it resulted only in mild albuminuria. [8]

Ravindran et al. conducted a retrospective cohort study of 374 patients with biopsy-proven membranous lupus nephritis, and performed immunohistochemistry studies on the kidney biopsy specimens against *EXT1* and *EXT2*. Patients *EXT1/EXT2*-positive were less likely to develop end-stage kidney disease, compared with those that were *EXT1/EXT2*-negative. A probable explanation is that exostosins produced in the GBM stimulate the synthesis of HS which has a positive effect on kidney function, proving the nephroprotective value of proper exostosin synthesis [9]. In the presented patient, no kidney biopsy was performed due to the lack of clinical indications and the parents' lack of consent due to the invasiveness of the procedure. Nevertheless, in the case of subsequent relapses, a kidney biopsy will be considered. Such rare cases as the presented patient are clinically challenging because of the few reports of NS in patients with HME; it is therefore difficult to predict the course of the disease in the presented case.

Steroid treatment not only provides remission of NS, but also reduces inflammation caused by lesions and pressure exerted on surrounding tissues. However, patients with frequent relapses of NS need multiple courses of steroids that may result in serious side-effects, such as obesity, hypertension, growth failure, and osteopenia [10]. The latter may increase the risk of fractures in bones susceptible to damage. As far as is known, in the skeletal manifestations of HME, the further course of NS in the affected patients remain enigmatic.

Due to the highest specificity, genetic evaluation seems to be indispensable in the postnatal screening of children of affected individuals. Early diagnosis, before the occurrence of the first symptoms, may improve long-term management [11].

In conclusion, it is hypothesised that the *EXT1* and *EXT2* mutations can cause renal glycocalyx alterations which lead to higher susceptibility to other NS risk factors.

SUMMARY

The presented patient is one of the few reported cases of NS in HME patients. While such coexistence is ultra-rare, the possibility of the interrelation of both disorders cannot be

excluded. The involvement of *EXT1* and *EXT2* gene mutations in extra-skeletal manifestations in HME patients is still poorly understood. Further studies of HS synthesis pathways may have important implications for understanding the pathologies related to altered glycocalyx.

Statement of Ethics

Written informed consent to publish the case with accompanying images was obtained from the mother of the affected patient.

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