Case Report

Prenatal diagnosis and molecular genetic analysis of short rib-polydactyly syndrome type III (Verma-Naumoff) in a second-trimester fetus with a homozygous splice site mutation in intron 4 in the NEK1 gene

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Abstract

Objective: To demonstrate perinatal imaging findings and to investigate the mutation in the NEK1 gene in a fetus with type III short rib-polydactyly syndrome (SRPS) (Verma-Naumoff).

Case Report: A 34-year-old woman with no past history of fetal SRPS was referred to the hospital at 21 weeks of gestation because of sonographic diagnosis of short limbs in the fetus. Fetal ultrasound revealed a narrow thorax, short ribs, short limbs with marginal spurs, and postaxial hexadactyly in both the hands and feet. A diagnosis of SRPS III (Verma-Naumoff) was made. Amniocentesis was performed. The karyotype was 46,XY. Molecular genetic analysis of the amniotic fluid cells identified a homozygous splice site mutation in intron 4 (c.331-1A>G) in the NEK1 gene. The parents were heterozygous for the mutation. The pregnancy was subsequently terminated and a malformed fetus was delivered with prominent forehead, a flattened nasal bridge, a narrow and short trunk, a protuberant abdomen, bilateral postaxial polydactyly and syndactyly of the hands and feet, and micromelic limbs. No facial cleft or genital abnormality was noted. The radiograph was consistent with SRPS III.

Conclusion: Polydactyly, micromelia, metaphyseal spurs, widened humeral metaphyses, and shortened ribs can be prominent prenatal ultrasound findings of SRPS III. The present case provides evidence for a correlation of a mutation in the NEK1 gene with SRPS III.

Keywords: NEK1; prenatal diagnosis; short rib-polydactyly syndrome type III; ultrasonography; Verma-Naumoff

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Introduction

Short rib-polydactyly syndromes (SRPSs) are a group of autosomal recessive osteochondrodysplasias caused by ciliary dysfunction and characterized by short ribs, polydactyly, short limbs, multiple abnormalities of the internal organs including kidneys, heart, liver, pancreas, genitalia, and intestines. Five types of SRPS have been recognized such as SRPS I (Saldino-Noonan; OMIM 263530), SRPS II (Majewski; OMIM 263520), SRPS III (Verma-Naumoff; OMIM 263510), SRPS IV (Beemer-Langer; OMIM 269860), and SRPS V (OMIM 614091). The different subtypes of SRPS may be a single genetic disorder with variable expressivity because of significant phenotypic overlap in different subtypes [1]. SRPS III (Verma-Naumoff) is characterized by polydactyly, micromelia, metaphyseal spurs and occasional situs inversus totalis [2,3]. Here, we present our experience of prenatal diagnosis and molecular genetic analysis of SRPS III in a second-trimester fetus associated with a homozygous splice site mutation in intron 4 in the NEK1 gene. Such an association is novel and has not been previously described.

Case report

A 34-year-old, gravida 3, para 1, woman had undergone amniocentesis at 17 weeks of gestation because of advanced maternal age, and the result revealed a karyotype of 46,XY. Her husband was 46 years old. The woman and her husband were non-consanguineous, and they had a healthy 6-year-old daughter. The woman had experienced spontaneous abortion twice, but cytogenetic analysis of the couple had revealed normal karyotypes. During this pregnancy, the pregnancy was uneventful until 21 weeks of gestation when level II ultrasound revealed a narrow thorax, short ribs, short limbs with marginal spurs, and postaxial hexadactyly in both hands and feet in the fetus (Fig. 1). The thoracic circumference (TC) was 12.17 cm (< 5th percentile), and the abdominal
circumference (AC) was 17.58 cm (75th percentile). The TC/AC ratio was 0.69. The lengths of the long bones were under the 5th percentile on nomograms. The femur, tibia, fibula, humerus, radius (curved) and ulna (curved) were measured 2.64 cm, 2.03 cm, 1.90 cm, 2.40 cm, 2.05 cm, and 2 cm, respectively. The biparietal diameter, head circumference and amniotic fluid amount were normal. Internal organs were unremarkable. A diagnosis of SRPS III (Verma-Naumoff) was made. Repeated amniocentesis was performed. Molecular genetic analysis of the amniotic fluid cells identified a homozygous splice site mutation in intron 4 (c.331-1 A > G) or IVS4-1 A > G in the NEK1 gene (Fig. 2). The parents were heterozygous for the mutation (Fig. 2). Molecular analysis of the amniotic fluid cells revealed no mutations in the DYNC2H1 gene. The pregnancy was subsequently terminated at 22 weeks of gestation. A 552-g male fetus was delivered with prominent forehead, a flat-nosed nasal bridge, a narrow and short trunk, a protuberant abdomen, bilateral postaxial polydactyly and syndactyly of the hands and feet, and micromelic limbs (Fig. 3). No facial cleft or genital abnormality was noted. Postnatal molecular analysis of the fetal tissues confirmed the prenatal diagnosis. The radiograph was consistent with SRPS III (Fig. 4).
a fetus with SRPS III. The present case provides evidence for a correlation of a mutation in the \textit{NEK1} gene with SRPS III.

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\section*{References}


