Taiwanese Journal of Obstetrics & Gynecology 53 (2014) 583–587

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Short Communication

Prenatal diagnosis and molecular cytogenetic characterization of a 1.07-Mb microdeletion at 5q35.2–q35.3 associated with *NSD1* haploinsufficiency and Sotos syndrome

Chih-Ping Chen [a, b, c, d, e, f, *], Chen-Ju Lin [a, g], Schu-Rern Chern [b], Yu-Peng Liu [h, i], Yu-Ling Kuo [j], Yen-Ni Chen [a], Peih-Shan Wu [k], Dai-Dyi Town [a], Li-Feng Chen [a], Chien-Wen Yang [b], Wayseen Wang [b, l]

[a] *Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan*
[b] *Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan*
[c] *Department of Biotechnology, Asia University, Taichung, Taiwan*
[d] *School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan*
[e] *Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan*
[f] *Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[g] *Department of Medicine, Mackay Medical College, New Taipei City, Taiwan*
[h] *Department of Radiology, Mackay Memorial Hospital Hsinchu Branch, Hsinchu, Taiwan*
[i] *Mackay Medicine, Nursing and Management College, Taipei, Taiwan*
[j] *Department of Obstetrics and Gynecology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[k] *Gene Biodesign Co. Ltd, Taipei, Taiwan*
[l] *Department of Bioengineering, Tatung University, Taipei, Taiwan*

ARTICLE INFO

Article history:
Accepted 29 October 2014

Keywords:
5q35 microdeletion
array comparative genomic hybridization
NSD1 haploinsufficiency
prenatal diagnosis
Sotos syndrome

ABSTRACT

Objective: To present prenatal diagnosis and molecular cytogenetic characterization of a *de novo* 5q35 microdeletion associated with Sotos syndrome.
Methods: This was the first pregnancy of a 29-year-old woman. The pregnancy was uneventful until 27 weeks of gestation when left ventriculomegaly was first noted. At 31 weeks of gestation, polyhydramnios, macrocephaly, and ventriculomegaly were prominent on ultrasound, and left pyelectasis and bilateral ventriculomegaly were diagnosed on magnetic resonance imaging. The woman underwent amniocentesis and cordocentesis at 32 weeks of gestation. Conventional cytogenetic analysis was performed using cultured amniocytes and cord blood lymphocytes. Array comparative genomic hybridization (aCGH) was performed on uncultured amniocytes and parental blood. Metaphase fluorescence *in situ* hybridization (FISH) was performed on cultured lymphocytes.
Results: Conventional cytogenetics revealed a karyotype of 46,XX. aCGH on uncultured amniocytes revealed a *de novo* 1.07-Mb microdeletion at 5q35.2–q35.3 encompassing *NSD1*. Metaphase FISH analysis on the cord blood lymphocytes confirmed the deletion at 5q35.2. The postnatal phenotype was consistent with Sotos syndrome.
Conclusion: Fetuses with Sotos syndrome may present macrocephaly, polyhydramnios, ventriculomegaly, and pyelectasis in the third trimester. aCGH and metaphase FISH are useful for rapid diagnosis of 5q35 microdeletion associated with Sotos syndrome.

Introduction

Sotos syndrome (OMIM 117550) is an autosomal dominant disorder that is characterized by cardinal features of macrocephaly with a high broad forehead, an inverted pear-like head, sparse

* Corresponding author. Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.
E-mail address: cpc_mmh@yahoo.com (C.-P. Chen).

http://dx.doi.org/10.1016/j.tjog.2014.10.002

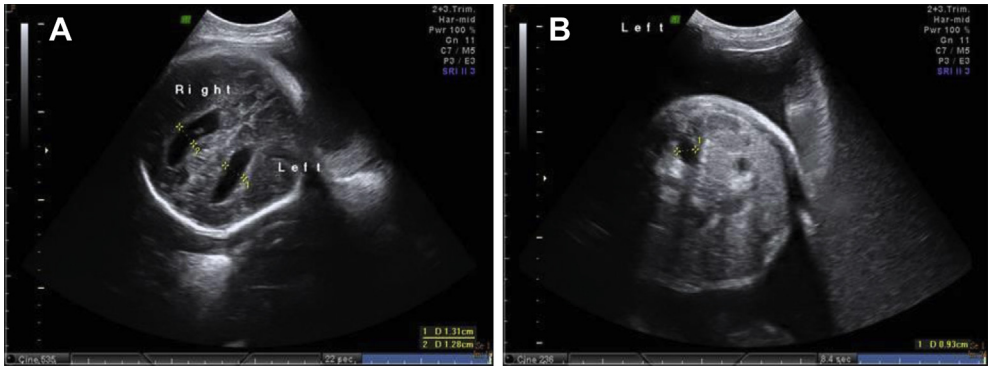

Fig. 1. Prenatal ultrasound at 35 weeks of gestation shows (A) ventriculomegaly and (B) left pyelectasis.

frontotemporal hair, molar flushing, down-slanting palpebral fissures, a long face, a pointed chin, learning disability, and overgrowth; major features of advanced bone age, abnormal X-ray findings of the skull, poor feeding, hypotonia, neonatal jaundice, seizures, scoliosis, cardiac and renal abnormalities, joint laxity, and pes planus; and minor features of neoplasm development such as sacrococcygeal teratoma, presacral ganglioma, neuroblastoma, acute lymphoblastic leukemia, small cell lung cancer, Wilms tumor, hepatocellular carcinoma, cardiac/ovarian fibroma, and germ cell tumor [1–5]. The incidence of Sotos syndrome is estimated to be 1:14,000 live births [5].

Prenatal diagnosis of Sotos syndrome associated with a *de novo* 5q35 microdeletion is very rare. Here, we present molecular cytogenetic characterization in such a case.

Materials and methods

Clinical description

This was the first pregnancy of a 29-year-old woman. Her husband was aged 28 years, and there was no family history of congenital malformations. The pregnancy was uneventful until 27 weeks of gestation when left ventriculomegaly (ventricular diameter = 1.3 cm) was first noted. At 31 weeks of gestation, polyhydramnios, macrocephaly (biparietal diameter = 8.87 cm; 33 weeks) and ventriculomegaly were prominent (Fig. 1). Magnetic resonance imaging at 31 weeks of gestation showed left pyelectasis and mild dilation of the ventricular diameter in bilateral temporal horns of lateral ventricles (left side = 1.5 cm; right side = 1.3 cm; Fig. 2). The woman underwent amniocentesis and cordocentesis at 32 weeks of gestation. Conventional cytogenetic analysis was performed using cultured amniocytes and cord blood lymphocytes. Array comparative genomic hybridization (aCGH) was performed using uncultured amniocytes. No cytogenetic abnormality was found by conventional cytogenetics. However, aCGH and metaphase fluorescence *in situ* hybridization (FISH) detected a 5q35 microdeletion. Sotos syndrome caused by chromosomal microdeletion was diagnosed. At 36 weeks of gestation, a 2800-g female baby was delivered with macrocephaly and characteristic craniofacial appearance of Sotos syndrome.

Conventional cytogenetic analysis

Routine cytogenetic analysis by G-banding techniques at the 550 bands of resolution was performed. Amniotic fluid and umbilical cord blood were collected, and the samples were subjected to cell culture according to the standard cytogenetic protocol.

aCGH

Whole-genome aCGH on the DNAs extracted from uncultured amniocytes derived from 10 mL of amniotic fluid and parental blood was performed using the NimbleGen ISCA Plus Cytogenetic Array (Roche NimbleGen, Madison, WI, USA), which has 630,000 probes and a median resolution of 15–20 kb across the entire genome according to the manufacturer's instruction. The DNA from uncultured

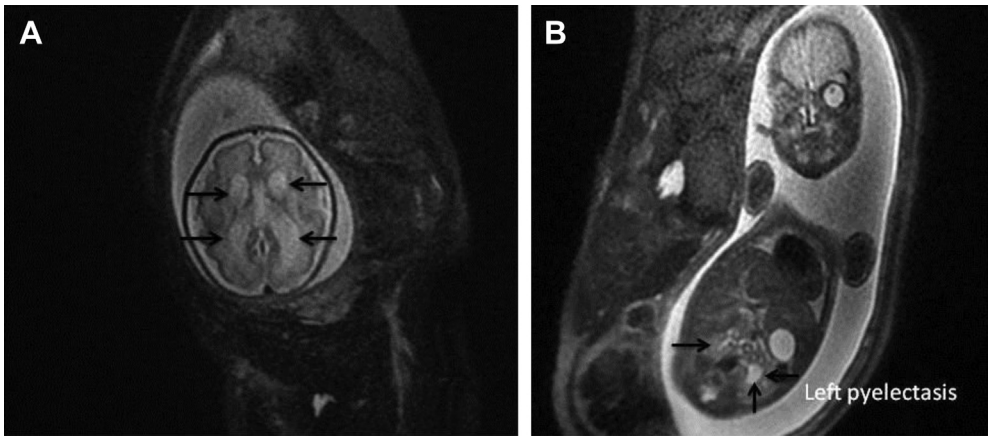

Fig. 2. Magnetic resonance imaging analysis at 31 weeks of gestation shows (A) mild dilation of bilateral lateral ventricles (arrows) and (B) left pyelectasis and a normal right kidney.