

Recurrent neural tube defects

Goh S L, Tan J V K, Kwek K Y C, Yeo G S H

ABSTRACT

We report a case of recurrent neural tube defects in a 30-year-old multigravida with no medical or family history of note. She presented with a significant history of having three (out of four) previous pregnancies affected by neural tube defects diagnosed at the 20-week foetal anomaly ultrasonographical scans, and which resulted in mid-trimester pregnancy terminations. Previous investigations for the foetuses did not yield any obvious cause. We discuss the possible differential diagnoses and aetiological factors. Rare causes of neural tube defects need to be excluded in recurrent cases with no obvious aetiology.

Keywords: anencephaly, encephalocele, folic supplementation, neural tube defects, ultrasonography

Singapore Med J 2006; 47(8):728-729

INTRODUCTION

Recurrent neural tube defects (NTD) have been reported previously in the literature, in association with syndromes as well as familial non-syndromic cases. We report a multigravida patient with a significant history of three previous pregnancies being affected by neural tube defects.

CASE REPORT

Our patient was a 30-year-old Malay woman, married for seven years, with four previous pregnancies. She had a significant history of three previous pregnancies having been affected by foetal anencephaly. She had no medical history of note, except for a previous cholecystectomy in 1998 for cholelithiasis. She had no family history of note and no history of ingestion of illicit drugs or traditional medicines. She was in a non-consanguineous marriage and all the pregnancies were with the same partner.

Her first pregnancy was in 1997 when she booked

late at 30.1-week gestation. Screening ultrasonography (US) performed then showed a mildly enlarged cisterna magna of 11 mm, with an absent inferior vermis. Repeat US at 37.7 weeks was done but the cerebellum was not seen due to advanced gestation. She remained otherwise antenatally well and delivered vaginally at term to a 3.17 kg female infant. Postnatal cranial US for the baby was normal. The baby was followed-up with normal developmental milestones, till six months of age when she was discharged.

She booked at 15-week gestation for her second pregnancy in 1998 and had screening US at 19.7 weeks. Anencephaly was diagnosed, with the abdominal circumference and femur length being less than the third centiles for gestational ages. No other foetal anomalies was detected. The patient and her husband opted for a mid-trimester termination of the pregnancy (MTPT) performed at 22-week gestation. On neonatal review following the abortion, the diagnosis of anencephaly was confirmed in a male foetus. The parents did not consent to a postmortem autopsy and no chromosomal study was done.

She booked at six weeks amenorrhoea for her next pregnancy in 2001, and had early first trimester dating scans at 6.0- and 10.3-week gestation. Early screening US was done at 15.4- and 16.3-week gestation, which showed anencephaly with an abdominal circumference of less than the third centile for gestational age. No other gross foetal anomalies were noted. MTPT was performed the week after the ultrasonographical diagnosis. The abortus was noted to be of male gender and anencephaly was confirmed. No chromosomal study or autopsy was performed, in line with the parents' request.

She booked at 15-week gestation for her fourth pregnancy in 2002, and early screening ultrasound at 16-week gestation showed an anechoic cyst on the posterior aspect of the foetal head. The cyst measured 24 mm by 15 mm. A defect was also noted in the occiput but the size was difficult to ascertain. It was noted that no cerebral tissue could be visualised within the cyst. Repeat screening US at 20.3-week gestation showed a skull bone defect at the posterior

Department of General
Obstetrics and
Gynaecology
KK Women's and
Children's Hospital
100, Bukit Timah Road
Singapore 229899

Goh S L, MBBS,
MRCOG
Associate Consultant

Department of
Maternal Foetal
Medicine

Tan J V K, MBBS,
MRCOG
Associate Consultant

Kwek K Y C,
MBBS, MRCOG,
MRANZCOG
Senior Consultant

Yeo G S H, MBBS,
FRCOG
Senior Consultant and
Chief

Correspondence to:
Dr Goh Shen Li
Tel: (65) 6394 1891
Fax: (65) 6298 6343
Email: shenligoh@
hotmail.com

vertex, with an encephalocele measuring 34 mm by 30 mm by 18 mm, and a lemon-shaped head with a dilated lateral ventricle of 13 mm. The cavum was absent and the rest of the structural review (notably the heart, spine and kidneys) was normal. A diagnosis of an occipital meningocele was made and the patient opted for a MTPT at 21-week gestation. A post-abortion review was made by the neonatologist who noted an occipital encephalocele in a male abortus. The parents again declined autopsy or chromosomal studies.

The patient had normal routine antenatal booking blood investigations, with unremarkable renal function tests and coagulation profile. The parents declined postmortem examinations for all three affected fetuses. It was noteworthy that all three affected fetuses were male, and that folic acid supplementation was prescribed to the patient at her booking visits in each pregnancy. She was not on any anti-folate medications. However, the patient did not start folic acid in the periconceptional periods between each pregnancy despite intensive counselling.

DISCUSSION

The recurrence risk of NTD with one affected sibling is 3.0%, and the recurrent lesion tends to be concordant with the first⁽¹⁾. This figure is useful in the genetic counselling of patients with a history of affected pregnancies. However, a previous retrospective analysis has also shown that in siblings affected by non-syndromal NTD, the NTD tend to occur at different levels (above or below vertebral level T12), with the exception of spina bifida⁽²⁾.

Although all the affected fetuses in this case were male, anencephaly is clearly not a sex-linked malformation and its aetiology is still being disputed⁽³⁾. There has been no suggestion from any reports so far regarding sex-linked dominance inheritance. There is evidence, however, of a major gene involvement in familial anencephaly with parental consanguinity, and is likely to be recessive in inheritance⁽⁴⁾. A single gene cause of recurrent NTD is the Meckel-Gruber syndrome⁽⁵⁾. It is a rare autosomal recessive disorder and carries a 25% risk of recurrence. Other features of this syndromic triad include polycystic kidneys and polydactyly.

Recurrent NTD have been reported to be associated with partial trisomy 2p22-pter⁽⁶⁾ and 20p⁽⁷⁾, resulting from a maternally-derived translocation. There is possibly a role of 2p24 triplication as well in the neural tube development, as this has been reportedly associated specifically with recurrent anencephaly⁽⁸⁾. This highlights the importance of chromosomal analysis in the aetiological exploration of NTD, and this can be easily ascertained by prenatal diagnosis. In this case, no parental chromosomal studies were performed to exclude chromosomal translocations.

Hyperhomocystinaemia has been associated with vascular disease, and the disturbance of maternal and

foetal homocysteine metabolism can lead to foetal NTD, pre-eclampsia, abruptio and recurrent pregnancy loss⁽⁹⁾. There have unfortunately been no strategies to date in relation to homocysteine metabolism that has been identified to reliably reduce the frequency of these problems. Methylenetetrahydrofolate reductase (MTHFR) genetic polymorphisms such as C677T and A1298C mutations⁽¹⁰⁾ are associated with hyperhomocystinaemia, and folate sufficiency is thought to play a role in the phenotypic expression of MTHFR mutations.

Folate supplementation has been shown to halve the risk of foetal NTD⁽¹¹⁾. Low doses (400 mcg) reduce the risk of first occurrences and high-dose supplementation (5 mg) prevents a high proportion of recurrent defects⁽¹²⁾. Ideally, folate supplementation should be started three months preconceptionally in the high-risk population. NTD have also been associated with low concentrations of cobalamin in amniotic fluid⁽¹³⁾, and both cobalamin and folate may be independent risk factors for neural tube defects.

In conclusion, the aetiology of recurrent NTD is varied and largely unknown. In this case, the patient has been advised to have pre- and periconceptional high-dose folic acid supplementation, to book early in her next pregnancy, and to have early screening US. Postmortems of any affected fetuses as well as parental karyotyping would be useful in the future management of this patient.

REFERENCES

- Cowchock S, Ainbender E, Prescott G, et al. The recurrence risk for neural tube defects in the United States: a collaborative study. *Am J Med Genet* 1980; 5:309-14.
- Drainer E, May HM, Tolmie JL. Do familial neural tube defects breed true? *J Med Genet* 1991; 28:605-8.
- Kasai K, Nakayama S, Shik SS, Yoshida Y. Sex selection and recurrence of anencephaly. *Int J Bio Res Pregnancy* 1982; 3:21-4.
- Shaffer LG, Marazita ML, Bodurtha J, Newlin A, Nance WE. Evidence for a major gene in familial anencephaly. *Am J Med Genet* 1990; 36:97-101.
- Tanriverdi HA, Hendrik HJ, Ertan K, Schmidt W. Meckel Gruber syndrome: a first trimester diagnosis of a recurrent case. *Eur J Ultrasound* 2002; 5:69-72.
- Doray B, Favre R, Gasser B, et al. Recurrent neural tube defects associated with partial trisomy 2p22-pter: a report of two siblings and review of the literature. *Genet Couns* 2003; 14:165-72.
- Zumel RM, Darnaude MT, Delicado A, et al. Trisomy 20p from maternal translocation and anencephaly. Case report and genetic review. *Ann Genet* 1989; 32:247-9.
- Winsor SH, McGrath MJ, Khalifa M, Duncan AM. A report of recurrent anencephaly with trisomy 2p23-2pter: additional evidence for the involvement of 2p24 in neural tube development and evaluation of the role for cytogenetic analysis. *Prenat Diagn* 1997; 17:665-9.
- Hague WM. Homocysteine and pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2003; 17:459-69.
- Isotalo PA, Wells GA, Donnelly JG. Neonatal and fetal methylenetetrahydrofolate reductase genetic polymorphisms: an examination of C677T and A1298C mutations. *Am J Hum Genet* 2000; 67:986-90.
- ACOG Committee Opinion: Committee on Obstetrics: Maternal and Fetal Medicine Number 120, March 1993. Folic acid for the prevention of recurrent neural tube defects. *Int J Gynaecol Obstet* 1993; 42:75-7.
- Eskes TK. Possible basis for primary prevention of birth defects with folic acid. *Fetal Diagn Ther* 1994; 9:149-54.
- Steen MT, Boddie AM, Fisher AJ, et al. Neural tube defects are associated with low concentrations of cobalamin (vitamin 12) in amniotic fluid. *Prenat Diagn* 1998; 18:545-55.