Reminder of important clinical lesson

Di Sala syndrome

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Summary

Di Sala syndrome or fetal warfarin syndrome/fetal warfarin embryopathy is a rare condition as result of fetal exposure due to maternal ingestion of warfarin during pregnancy. The authors report here a male infant with this condition whose mother was suffering from rheumatic mitral valvular heart disease for which she underwent prosthetic mitral valvular replacement surgery and put on injectable long acting penicillin and oral low-molecular weight anticoagulant drug (warfarin) for life long. The patient presented with facial dysmorphism, pectus excavatum, stippled epiphyses dolichocephaly, brachydactyly, polydactyly short neck and growth retardation. Shortened fourth metacarpal bones were also noted in this case which was not yet reported in literatures, to the best of our knowledge.

BACKGROUND

Low-molecular weight oral anticoagulant drug (warfarin) and its derivatives have disadvantages in mother and fetus in term of safety, efficacy and cost. It easily crosses the placenta and causes spontaneous abortion, stillbirth, neonatal death and many other congenital anomalies known as warfarin syndrome/warfarin embryopathy or Di Sala syndrome.

CASE PRESENTATION

An 11-month-old male infant was referred to us in our medical university for evaluation of delayed milestones, stunted growth and no vision. His maternal history was significant. His mother was suffering from rheumatic valvular heart disease for which prosthetic mitral valve

replacement was done in 2002. She was put on injectable long acting penicillin (penidure) and low-molecular weight oral anticoagulant (warfarin) for life long. However mother delivered a male child in May 2010 against medical advice. The baby patient was born at 35 weeks gestation and developed hypoxic ischaemic encephalopathy and revived with the help of ventilatory support.

Physical examination revealed stunted growth of the patient, depressed nasal bridge, deep recess between ala of nose and upper lip, telecanthic eyes (figure 1A,B) and pectus excavatum. Brittle nails, brachydactyly, polydactyly were present in the left fifth finger (figure 2). Ophthalmological examination revealed normal bilateral optic disc but no vision, as the baby was unable to follow torch light. Audiometric findings were normal.

Figure 1 (A, B) Coloured photographs of 11-month-old male patient of Di Sala syndrome in profile (A) and enface views (B) revealed – depressed nasal bridge, deep recess between ala of nose and upper lip and telecanthic eyes.

INVESTIGATIONS

Digital skiagram of skull including face revealed brachycephalic head, nasal hypoplasia and narrowed nasopharyngeal airway (figure 3). Antero-posterior view of bilateral knee joints revealed stippled metaphyses and epiphyses with calcifications in epiphysial regions of lower ends of femur and upper ends of tibia (figure 4). Lateral view

Figure 2 Coloured photograph of left hand of 11-month-old male patient of Di Sala syndrome revealed- brittle nails (small open arrows head), brachydactyly and additional phalanx in fifth finger (open arrow).

of chest skiagram revealed patchy small calcification in sternum with evidence of pectus excavatum (figure 5). Antero-posterior view of left hand skiagram revealed brachydactyly, additional phalange in fifth finger and shortened fourth metacarpal bones were also noted in this case which was not yet reported in literatures to the our best of knowledge (figures 6 and 7). MRI of brain did not reveal any obvious abnormality. However MRI of both orbit revealed atrophic bilateral optic nerves (figure 8). Two-dimensional echocardiography also did not reveal any obvious cardiac defect. Above classical clinico-radiological

Figure 3 Digital skiagram of head (lateral view) of 11-month-old male patient of Di Sala syndrome revealed-brachycephalic head, nasal hypoplasia and narrowed nasopharyngeal airway (between two open arrow head).

Figure 4 Digital skiagram of bilateral knee joint (antero-posterior view) of 11-month-old male patient of Di Sala syndrome revealed- stippled metaphyses (curved solid arrow) and epiphyses. Calcifications in epiphysial regions of lower ends of and upper end of tibia femur (straight solid arrow).

Figure 5 Digital chest skiagram (lateral view) of 11-month-old male patient of Di Sala syndrome revealed-patchy small calcification in sternum (open arrows) with evidence of pectus excavatum (open arrow head).

findings were consistent with Di Sala syndrome or fetal warfarin syndrome.

DIFFERENTIAL DIAGNOSIS

Chondrodysplasia punctata.

TREATMENT

Symptomatic. If pregnancy cannot be avoided, switch over to high-molecular weight anticoagulant drug (heparin) which is unable to cross placental blood barrier.

OUTCOME AND FOLLOW-UP

Prognosis depends on severity of defects acquired inutero. Infant presenting with upper airways obstruction can be relieved by oral intubation. CNS abnormalities often have poor prognosis.

DISCUSSION

The first case of fetal warfarin embryopathy was reported in 1966 by Di Sala hence, it is also known as Di Sala syndrome. Anomalies include nasal hypoplasia, choanal atresia, laryngeal abnormalities, upper airway obstruction, short neck, hypoplastic distal phalanges, brachydactyly and short limbs.^{1 2} Extensive thorough search of literatures have been revealed, that we are reporting a third post natal alive case of infant with Di Sala syndrome from Asia. Shortened fourth metacarpal bones were noticed in this case which was not yet reported in literatures, to the best of our knowledge (figures 6 and 7). Warfarin, a coumarin derivative, is a low-molecular weight oral anticoagulant. It is mainly indicated for prophylaxis of venous thromboembolic disease and systemic embolism associated with

Figure 6 Digital skiagram of left hand (postero-anterior view) of 11-month-old male patient of Di Sala Syndrome revealed-Brachydactyly, shortened fourth metacarpal (star) and polydactyly in the fifth finger (open arrow head).

Figure 7 Digital skiagram of right hand (postero-anterior view) of 11-month-old male patient of Di Sala syndrome revealed-brachydactyly and shortened fourth metacarpal bone (star).

Figure 8 Axial T1 weighted MRI (TR-400 ms, TE-14 ms, FOV-16×16, thickness-3 mm and bandwidth 15.6 kHz) of orbit of 11-month-old male patient of Di Sala syndrome revealed-atrophied bilateral optic nerves (open arrows).

valvular heart disease or prosthetic heart valve. Warfarin and its derivatives have disadvantages in mother and fetus in term of safety, efficacy and cost. Low-molecular weight warfarin sodium easily crosses the placenta and causes spontaneous abortion, stillbirth, neonatal death and many other congenital anomalies known as Di Sala syndrome or warfarin syndrome/warfarin embryopathy.³

Warfarin is the preferred drug for prevention of systemic thrombo-embolism. However; it also has teratogenic effects in humans. Warfarin, being a low-molecular weight oral anticoagulant (about 1000 Daltons) easily crosses the placenta and reaches the fetal circulation causing warfarin embryopathy by blocking the recirculation of vitamin K leading to deficiency of vitamin K, which results in decreased level of vitamin K dependent clotting factor (II, VII, IX, X) synthesis resulting in haemorrhages in fetal organs. Secondly, it interferes in vitamin K reductase activity which leads to decrease in vitamin K dependent mineralisation inhibitors (osteocalcin and Gla matrix protein) in cartilage resulting in ectopic calcium deposits in epiphysis and epiphyseal stippling.^{2 4 5} Apart from this, it is also causing premature closure of growth plate resulting in shortening of extremities. Franco *et al* suggested that warfarin may inhibit arylsulfatase enzyme activity, the cause of X linked recessive chondroplasia punctata, which is phenotypically similar warfarin embryopathy.⁶

These warfarin effects occur in first trimester of pregnancy. The greatest susceptibility to warfarin embryopathy is between 6th and 9th weeks of gestational periods. Other teratogenic effects like optic atrophy, blindness, deafness, microcephaly, hydrocephalus, Dandy Walker malformation and mental retardation occur in second and third trimester of pregnancy. Low-molecular weight oral anticoagulant (warfarin) did not affect all fetuses of mother during high susceptible gestational periods.²

After reviewing 418 pregnancies with maternal ingestion of warfarin, Hall *et al*¹ concluded that live birth occurs in 83.7%, spontaneous abortion in 8.6%, stillbirths in 8.4%. premature deliveries in 4.6% and neonatal death occurred in 2.9% of these cases.

To avoid Di Sala syndrome, oral anticoagulant warfarin drug which readily crosses the placenta due to its lower molecular weight, mother should strictly avoid conception or switch over to high-molecular weight anticoagulant (heparin-20 000 Dalton) throughout pregnancy.⁷ Prognosis of warfarin syndrome depends on severity of defect occurred in utero.

Learning points

- ▶ Above case report alerts the clinicians to the teratogenic effects of warfarin. Pregnancy should be avoided in patients who are ingesting warfarin drug.
- ▶ Some of the findings can be detected in affected fetus in utero by ultrasonography around 25 weeks of gestation.
- ▶ Extensive thorough search of literatures have been revealed that we are reporting a third post natal alive case of infant with Di Sala syndrome from Asia.
- ▶ Shortened fourth metacarpal bones were reported first time in this case which was not yet reported in any literatures, to the best of our knowledge.

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Competing interests None.

Patient consent Obtained.

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