

Long-surviving Neu-Laxova syndrome confirmed by whole exome sequencing: a case report

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Case presentation

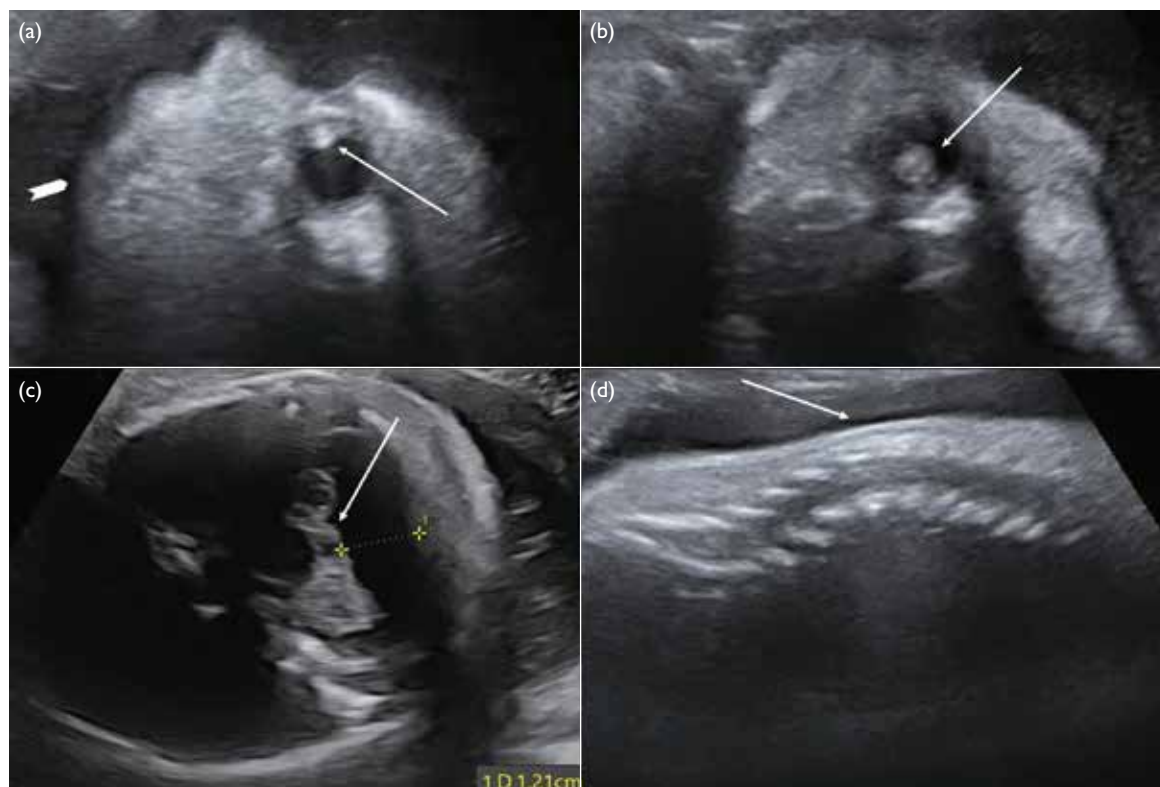
A 23-year-old pregnant nulliparous Pakistani woman underwent first-trimester Down syndrome screening in July 2019 that deemed her low risk with normal nuchal translucency. She did not have any morphology scan. At 34 weeks of gestation her uterus was considered small-for-dates. Ultrasound determined that her fetus had intrauterine growth restriction and multiple abnormalities. There was severe microcephaly (corresponding to only 24 weeks of gestation), Dandy-Walker malformation, bilateral cataracts, micrognathia, abnormal spinal curvature, and multiple joint contractures with bilateral clenched hands (Fig 1). On further enquiry, the patient disclosed that she and her husband were first cousins. The risk of the fetus having chromosomal abnormalities or autosomal recessive disease due to consanguinity was explained to the couple but they declined amniocentesis. Serial ultrasound scans showed poor interval growth. Subsequently the patient had spontaneous onset of labour at 40 weeks of gestation and delivered a female baby weighing 1.53 kg. The baby was apnoeic and had bradycardia requiring cardiopulmonary resuscitation for 6 minutes after birth.

The baby was confirmed to have multiple abnormalities similar to the prenatal ultrasound findings: microcephaly, Dandy-Walker variant, bilateral dense cataracts and microphthalmia, persistent arthrogryposis with joint deformities and contractures, and bilateral lung hypoplasia. Initially the limbs were oedematous with skin breakages that subsequently evolved into ichthyosis (Fig 2). Cord blood was sent for chromosomal microarray after delivery and showed several regions of >10 Mb long contiguous stretches of homozygosity consistent with the known consanguineous relationship of the couple

but there were no copy number of changes detected. Whole exome sequencing (WES) was performed due to suspected syndromal disease and confirmed the diagnosis of Neu-Laxova syndrome (NLS) with homozygous NM_006623.3(PHGDH):c.488G>A p.(Arg163Gln) missense variant. The parents were both heterozygous carriers. The child is now >3 years old (42 months of age at the time of writing). She has required a tracheostomy and mechanical ventilation since the age of 6 weeks. She is non-ambulatory and cannot sit without support. She has hearing and visual problems and cannot vocalise. She is fed via a Ryle's tube and has remained an in-patient in paediatric intensive care unit since birth.

Discussion

Neu-Laxova syndrome is a lethal autosomal recessive disorder characterised by neuro-oculo-ectodermal dysplasia with central nervous system malformations (dominated by microcephaly), ocular defects (eg, proptosis), craniofacial dysmorphism (eg, micrognathia, flattened nasal bridge, and hypertelorism), limb abnormalities (eg, arthrogryposis), ichthyotic skin changes, and intrauterine growth restriction. The fetus in our case had typical features of NLS on prenatal ultrasound (microcephaly, Dandy-Walker malformation, ocular defects of congenital cataract, micrognathia, multiple joint contractures, and intrauterine growth restriction). This syndrome is caused by mutation in either one of the three genes involved in the serine biosynthesis pathway: phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase 1 (PSAT1) or phosphoserine phosphatase (PSPH) that are essential for synthesis of brain lipids. Up to 2022, 88 cases of NLS had been reported with 45% related to consanguinity.¹ The



early cases reported were diagnosed clinically and by histopathological examination and following the emergence of molecular genetic diagnosis in 2014 by WES.¹

Chromosomal microarray can detect only

copy number changes (gains or losses), not gene mutations. This case illustrates the usefulness of molecular diagnosis by WES for a baby with multiple congenital abnormalities. The diagnosis can be quickly established and the prognosis of

the baby can be explained to the parents with appropriate supportive counselling. Molecular diagnosis is also helpful to verify parental carrier status so that the risk for future pregnancies can be predicted. In this case, with both parents a carrier, the risk of recurrence in any future pregnancy is 25%. Prenatal diagnosis by chorionic villus sampling or amniocentesis should be offered, and the option of termination of pregnancy should be discussed if the fetus is affected. Alternatively, pre-implantation genetic testing can be offered to select unaffected embryos and avoid a recurrently affected pregnancy. Since April 2021, a publicly funded prenatal genomic sequencing programme for antenatally diagnosed fetal structural anomalies has been available in the Hospital Authority. Pregnant women are considered eligible if the chromosomal microarray results are normal and if fetal abnormalities are considered by an expert panel to have high possibility of genetic aetiology.² Although publicly funded postnatal genomic sequencing is available for newborn babies and children, the test is usually performed only in highly selected cases and the turnaround time is often substantial. The WES in our case was performed by The University of Hong Kong in a research setting. There will be a need to enhance the provision of such services to meet the expanding clinical demands.

A local study found that consanguineous couples have an increased risk of autosomal recessive diseases in their offspring with an odds ratio of 8.7.³ A mid-trimester morphology scan should be performed to screen for fetal structural anomalies, and expanded carrier screening is advised for consanguineous couples prior to conception. Different pregnancy options can then be discussed, including pre-implantation genetic testing if both parents are a carrier of the same autosomal recessive disease. The expanded carrier screening panel that is available in Hong Kong includes the *PHGDH* gene responsible for NLS in our patient. If such screening had been performed before conception, the carrier status of the couple would have been identified. The observed positive carrier frequency of autosomal recessive diseases in the Chinese population has been reported as high as 58.7% overall (47.6% after excluding thalassaemias) in a local cohort.⁴ If resources allow, expanded carrier screening can be offered to all couples who wish to conceive, even in the absence of known consanguinity.

Neu-Laxova syndrome is a lethal disorder with most affected babies stillborn or dying soon after birth. The longest survival previously reported is 10 months of age.⁵ A case report in 2013 described a collodion baby who survived to 8 years of age with facial dysmorphism, limb anomalies, pachygyria and

genital hypoplasia, but without the most common features of microcephaly or intrauterine growth restriction, who was diagnosed clinically to have a mild form of NLS without molecular diagnosis.⁵ Our patient has the longest survival among the confirmed NLS cases reported in the literature.

In conclusion, WES can help establish a quick and accurate diagnosis of NLS in a baby with multiple structural abnormalities. Expanded carrier screening is advised for at-risk couples before conception to verify their carrier status and enable counselling about future pregnancy risks and options.

Author contributions

Concept or design: CW Kong.

Acquisition of data: YY Li.

Analysis or interpretation of data: All authors.

Drafting of the manuscript: CW Kong.

Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

The patient was treated in accordance with the Declaration of Helsinki. Written consent was obtained for publication of this article and accompanying images.

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