CASE REPORT

The effects of microduplication 1q21.1 and in-utero isotretinoin exposure

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SUMMARY

The impact of in-utero isotretinoin exposure has been widely reported, with many affected pregnancies failing to reach term.^{1,2} Due to the low numbers of in-utero isotretinoin exposed pregnancies, the interactions between this drug and rare genetic defects such as microduplication 1q21.1 are unclear, particularly how they might manifest phenotypically. We present this case of in-utero isotretinoin exposure occurring in a child with microduplication 1q21.1. The child was born with congenital abnormalities which did not fit into a single syndrome. Regrettably in-utero exposure to isotretinoin continues to occur. We hope this case will trigger further discussion on the dangers of dispensing Isotretinoin without ensuring stringent pregnancy testing and its potential interaction with genetic abnormalities, in particular with microduplication 1q21.1.

BACKGROUND

According to the most recent BINOCAR report, the total rates of congenital abnormality in the UK from 2007 to 2011 have decreased from 267/100 000 to 250/100 000.³ Chromosomal anomalies were responsible for a provisional incidence of 43/100 000 total births and non-chromosomal anomalies counted for 184/100 000 births.³ Microduplication 1q21.1 is a rare genetic anomaly affecting 3/10 000 of the general population.⁴ It presents with a spectrum of phenotypical features. Isotretinoin is a first-generation retinoid used to manage different forms of acne including the severe cystic acne. It also has been used in other skin conditions such as rosacea and lupus erythematosus.^{2,5} Retinoid agents are classified as first, second or third generation and are used in the treatment of various dermatological conditions.^{5,6}

Like all retinoids, isotretinoin is highly teratogenic; it has been suggested that 35% of babies exposed to isotretinoin in utero beyond day 15 postconception suffering from birth defects.¹ High congenital abnormality and miscarriage rates have led to all women taking isotretinoin being entered into the Pregnancy Prevention Programme.^{2,6,7} We present this case of a female child with a genetic abnormality, microduplication 1q21.1–1q21.2 and who was also exposed to Isotretinoin in utero.

CASE PRESENTATION

A 5-month-old, female Caucasian was delivered at term to healthy, non-consanguineous parents with a complex array of congenital malformations. Her phenotypically normal mother was prescribed

Isotretinoin for severe acne which she took from weeks 3–5 of pregnancy and discontinued once she found she was pregnant. The prenatal ultrasound scans revealed a cleft lip and cleft palate. The baby was delivered at term weighing 2.49 kg (5lb 8oz). She spent the first 17 days on invasive ventilation on the neonatal unit and a further day on high-flow oxygen.

She was found to have a boneless fibrous band, connecting the roof to the base of her mouth. This was later resected surgically. She was then transferred to a tertiary centre for MRI of the head and neck on day 10 of life. This showed a left-sided choanal atresia, nasal septum deviation and micrognathia. On day 13, a surgical examination under anaesthetic revealed an incomplete upper left lip, bifidity of the anterior two thirds of the tongue and a small oropharynx; following examination, a tracheostomy was also fitted. She also has a teratoma of the palate which contained a neonatal tooth. She had a left-hand syndactyly involving the third, fourth and fifth digits and second and third toe syndactyly on both feet. She had no congenital heart defect, no coloboma and no external ear defects. Her weight was between the 0.4 and the second centiles, her length and head circumference were between the second and the ninth centiles. She had social smiles and a good palmar grasp but could neither sit unsupported nor roll over. There was no family history of any congenital defects, including cleft lip or palate, nor of any other craniofacial or other syndromic abnormality.

INVESTIGATIONS

Microarray analysis of the child and her mother has been performed and revealed a microduplication, 1q21.1–1q21.2. The size is estimated to be between 1.92 Mb (DNA positions: 145799573–147721840) and 2.09 Mb (DNA positions: 145729355–147824178). A maternal FISH study confirmed that the 1q21.1 DNA gain was inherited from her mother.

The patient's mother is phenotypically normal. The paternal genetic testing was normal. The proband has two half siblings on the paternal side who are phenotypically normal but have not undergone genetic testing.

DIFFERENTIAL DIAGNOSIS

Genetic testing revealed the presence of microduplication 1q21.1–1q21.2 which partially explains the presenting features of this case. Another differential diagnosis which cannot be ruled out is CHARGE syndrome: features of CHARGE syndrome which this patient has presented with are choanal atresia, cleft lip, cleft palate and syndactyly.⁸ Although our patient

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had no congenital heart defect, no coloboma and no external ear defects, patients rarely present with all features of CHARGE syndrome, and this would have been unlikely to be picked up on an array as most cases are nonsense or frameshift mutations on CHD7.⁸ Fetal teratogen syndrome is a diagnosis of exclusion but again, could partly explain this infant's presentation.

OUTCOME AND FOLLOW-UP

At this stage, no further surgery has been performed, although insertion of a gastrostomy tube is planned to aid feeding prior to surgical repair of her cleft lip and palate at a later stage.

Further genetic testing such as the whole exome sequencing would be helpful to identify single base changes in the coding regions. However, it was felt the priority at 5 months was to optimise growth to allow surgical procedures (eg, gastrostomy) while accommodating parental sensitivity regarding further testing. Several admissions to the paediatric high dependency unit, mainly due to viral respiratory illnesses, has further slowed the follow-up process.

DISCUSSION

Microduplication 1q21.1–1q21.2 means genetic material has been added to the long arm of chromosome 1. This genetic abnormality is rare, with approximately 3/10 000 members of the general population being affected.⁴ It can occur spontaneously or may be inherited and is an autosomal dominant condition with a widely variable phenotype. It can cause problems including mild-moderate learning delay, macrocephaly, autism, behavioural problems, seizures, mild dysmorphism and heart problems.⁴ There is a very wide-ranging phenotype seen in microduplication 1q21.1; some believe there are further genetic or environmental factors which may cause the expression of a more extreme phenotype, although their nature is unknown.⁴ As this child is very young, it cannot be predicted which of these phenotypical manifestations she may develop.

While this child does have an underlying genetic anomaly inherited from her mother, which could partly explain her complex problems, the impact of in-utero exposure to Isotretinoin in early pregnancy cannot be underestimated. Isotretinoin is a vitamin A retinoid, used as a last-line treatment for severe cystic acne.² According to the literature, Isotretinoin affects the HOX-signalling pathways which play a role in the formation of the branchial arches during week 4 of embryogenesis.²

Days 21–35, the time when this case was exposed to isotretinoin in utero, are critical periods in organogenesis.⁷ In terms of head and neck development, the pharyngeal arches, precursors of the branchial arches begin forming on day 22, with facial formation occurring in weeks 4–10.⁷ Thus, the presence of a known teratogen during this period could have influenced branchial arch development. Children born with fetal retinoid syndrome often have issues with structures which are derived from the branchial arches including the heart, craniofacial formation and the central nervous system (CNS).^{5,7}

Features in this child which are suggestive of fetal retinoid syndrome include hypertelorism, cleft lip and palate, facial dysmorphism, micrognathia and syndactyly.¹ Fetal retinoid syndrome is known to present with a range of abnormalities, of varying severities¹ such as craniofacial defects, cardiovascular defects, neurodevelopmental problems due to CNS defects and abnormalities of the thymus.⁹ The craniofacial abnormalities include microtia and anotia, micrognathia, frontal upsweep, hypertelorism, flat nasal bridge and cleft palate; the cardiovascular defects include various conotruncal heart defects and aortic arch abnormalities; the CNS abnormalities include hydrocephalus, fourth-ventricle cyst, holoprosencephaly and microcephaly, cerebellar hypoplasia, cerebellar vermis agenesis, spina bifida and learning difficulties; the thymus

abnormalities include ectopia, hypoplasia and aplasia.⁹ Comprehensive descriptions including less common defects have been published in the literature.^{1,10}

While the abnormalities described in this case cannot be fully attributed to any single syndrome, it is possible that the combination of the microduplication, and alongside in-utero exposure to Isotretinoin may partially explain this presentation. However, the fibrous band, choanal atresia and teratoma cannot be explained by either cause. CHARGE syndrome could be an alternative diagnosis. However, the paucity of major diagnostic criteria would rather suggest an atypical presentation. Further genetic testing (CHD7) is being considered for the future. Hence, there must be another cause for this case, which is, as yet, unexplained. As the child continues to develop, we may gain a better understanding as to the true extent of her problems. In the meantime, it is important to continue to monitor this child for developmental, cardiac and neuropsychiatric problems. This case also stresses further the importance of stringent pregnancy testing in women of childbearing age when dispensing isotretinoin.

Learning points

- Exposure to isotretinoin in-utero is an uncommon but important presentation in paediatrics.
- Genetic variants, such as microduplication 1q21.1, may be an important factor in susceptibility to in-utero teratogen exposure and could help explain why not all teratogen-exposed pregnancies do result in affected offspring.
- In light of this case, it is vital to reinforce the importance of stringent pregnancy testing in women of childbearing age prior to the prescription of a known teratogen such as isotretinoin.

Contributors SKT wrote the article under the guidance of RT. RT reviewed the article and made corrections and sought consent from the patient's guardian.

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