Opitz oculo-genito-laryngeal syndrome: a rare cause of recurrent aspiration pneumonia in an adult

Deepthi de Silva, Aileen Osborne, Sheila A Simpson, John C S Dean, Anthony Seaton

Abstract

A 64 year old woman presented with persistent and severe symptoms due to recurrent aspiration pneumonias associated with oesophageal reflux. She had had multiple miscarriages and her son at birth had widely spaced eyes (hypertelorism), hypospadias, bilateral undescended testes, and an imperforate anus. Her daughter has mild hypertelorism and her daughter’s son had neonatal inspiratory stridor, hypospadias and hypertelorism, all features now recognised as typical of the Opitz oculo-genito-laryngeal syndrome. This syndrome is genetically heterogeneous with autosomal dominant (linked to chromosome 22q21) and X-linked (linked to Xp22) inheritance. This family’s history and genetic linkage data are consistent with linkage to Xp22. The proband is a manifesting carrier of this syndrome; her history of recurrent aspiration is probably secondary to pharyngeal neuromuscular incoordination aggravating gastro-oesophageal reflux. Obtaining a family history gives a vital clue to the diagnosis of Opitz oculo-genito-laryngeal syndrome. It is also suggested that this condition should be included in the differential diagnosis of recurrent aspiration pneumonia.

Case report

A 64 year old ex-teacher presented in 1989 with a six month history of cough, wheeze and recurrent febrile episodes, resistant to several courses of antibiotics. The cough and wheeze were initially nocturnal and were helped by sitting up. She denied symptoms of reflux. Her sputum had been purulent and she had lost 5 kg in weight. The chest radiograph showed consolidation at the right base and a small pleural effusion. Pulmonary function showed moderate airflow obstruction with normal gas transfer. Barium swallow showed a small sliding hiatus hernia, and bronchoscopic examination revealed oedematous, inflamed airways with purulent secretions. Chronic inflammatory cells were seen on bronchial biopsy specimens. Treatment with bronchodilators and a trial of corticosteroids produced no benefit and she developed more extensive bilateral basal shadow, lost more weight, and recorded intermittent fevers of 40°C. Further barium studies showed reflux, a computed tomographic (CT) scan showed basal bronchiectasis, and her ESR was raised. Because of the possibility of an arteritic condition, open lung biopsy specimens were taken but showed only chronic inflammatory changes and no food particles. A diagnosis of recurrent aspiration pneumonia was made and, ultimately, long term antibiotics and anti-reflux treatment controlled the worst of her symptoms. She has remained active, but with several less severe recurrences, for the last five years.

At initial presentation it was noted that she had had three first trimester miscarriages and a stillbirth, in addition to having two live born children, but her widely spaced eyes were not appreciated. Her brother had died aged 19 after cardiac surgery. Her son, now aged 34, had multiple congenital anomalies at birth, including hypospadias, undescended testes, imperforate anus and hypertelorism, but no stridor or aspiration. He is now in good health but has severe myopia with a horizontal split in Descemet’s membrane suggestive of arrested congenital glaucoma. Her daughter, now aged 31, has a multiple impulse personality disorder. Of her two sons, the first had inspiratory stridor at birth (resolving in the first few months of life), hypospadias, hypertelorism, a widow’s peak of the anterior hairline, a prominent metopic ridge, lingual frenulum and a short, bulbous nose with anteverted nares (fig 1). The second has a normal appearance and is well.

Lymphocyte chromosome analysis at metaphase in the proband’s son and grandson was normal. Genomic DNA was obtained using standard protocols. A DNA linkage study was performed using microsatellite markers on chromosomes 22q11 (d22s257, d22s345, and...
syndrome which affects multiple midline structures and is characterised by hypertelorism, hypospadias, and laryngeal dysfunction. Additional reported features include cleft palate, bifid uvula, congenital heart defects, renal or ureteral anomalies, anal atresia, scalp defects, midline brain anomalies, and mental retardation.1–3 Affected infants with the syndrome are at risk of respiratory and swallowing difficulties related to either structural (tracheo-oesophageal clefs or fistulae) or functional (neuromuscular incoordination of swallowing) abnormalities.4 In some instances the recurrent aspirations or severity of the structural anomalies have resulted in neonatal or childhood deaths. Recent evidence5 has shown this to be a genetically heterogeneous condition, with both an autosomal dominant form linked to chromosome 22q11.2 and an X-linked form linked to Xp22. The clinical features appear to overlap, although the X-linked form has a characteristic mid face consisting of a short nose with anteverted nares.6

Two features in this family have not previously been reported as part of the syndrome: the personality disorder in the daughter (which may be coincidental, although adults with 22q11 microdeletions are known to manifest psychiatric disorders including psychosis7) and the corneal abnormality in the son. A literature review has not revealed any cases in which an adult, as opposed to a child, first presented with recurrent aspiration. In our proband we suspect that oesophageal reflux developing late in life, acting in combination with the chromosome 22q11.2 haplotype 2,3,1 segregating with the disease). Note the possible recombination between markers d22s257 and d22s345 in II.3. Markers which failed to amplify are denoted with a dash.

Discussion

This family's history of congenital anomalies is typical of the Opitz oculo-genito-laryngeal syndrome, sometimes designated G or BBB after the initials of the original families.1 It is a syndrome which affects multiple midline structures and is characterised by hypertelorism, hypospadias, and laryngeal dysfunction. Additional reported features include cleft palate, bifid uvula, congenital heart defects, renal or ureteral anomalies, anal atresia, scalp defects, midline brain anomalies, and mental retardation.1–3 Affected infants with the syndrome are at risk of respiratory and swallowing difficulties related to either structural (tracheo-oesophageal clefs or fistulae) or functional (neuromuscular incoordination of swallowing) abnormalities.4 In some instances the recurrent aspirations or severity of the structural anomalies have resulted in neonatal or childhood deaths. Recent evidence5 has shown this to be a genetically heterogeneous condition, with both an autosomal dominant form linked to chromosome 22q11.2 and an X-linked form linked to Xp22. The clinical features appear to overlap, although the X-linked form has a characteristic mid face consisting of a short nose with anteverted nares.6

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