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CASE REPORT

Congenital heart block associated with undiagnosed maternal Primary Sjögren's Syndrome – a case report and discussion

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Congenital heart block (CHB) has been linked with Sjögren's Syndrome. This paper reports a case of previously undiagnosed maternal Primary Sjögren's Syndrome (1°SS) that was only discovered following the birth of the patient's first child with CHB. The possible pathophysiological mechanisms underlying CHB associated with 1°SS are discussed.
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Case report

A 32-year-old caucasian female was referred by a rheumatologist to the Oral Medicine unit for investigation of possible Primary Sjögren's Syndrome (1°SS). The patient had given birth to a baby girl, who was diagnosed post-delivery with heart block requiring pacemaker insertion. Serological investigations of this lady revealed positive Ro, La, ANA and rheumatoid latex antibodies.

The patient had been diagnosed with hypothyroidism which was managed initially with thyroxine 50 μg daily and this dose had been increased to 150 μg. The patient reported no symptoms of dry mouth or ocular dryness/irritation and gave no history of salivary gland swelling.

General examination revealed no evidence of connective tissue disease and there was no swelling or tenderness of the salivary glands. The oral mucosa appeared moist and all salivary ducts were patent and expressed clear saliva.

Special investigations included sialometry and a Schirmer's eye test. Whole mouth saliva was collected under standardized conditions (as described by Valdini and Sreebny, 1987) and the unstimulated salivary flow rate was measured at 0.24 ml min^{-1}; this was considered to be within the normal range. The Schirmer's tests were both negative. A labial gland biopsy was undertaken and the histopathology was consistent with an autoimmune sialadenitis (focal score 2.1/4 mm^2). Despite immunological evidence of Sjögren's Syndrome, at this stage there were no subjective symptoms or objective signs of dry eyes/mouth which would meet the revised European criteria (Vitali *et al*, 2002) for the classification of 1°SS.

Sialometry remained within normal limits at yearly follow up appointments. A second female child was born 2 years after the first, without congenital heart block (CHB). Following this second birth, the patient developed ocular symptoms (dry, gritty eyes) and was subsequently referred to an ophthalmologist, who found that the Schirmer's test for both eyes was positive and the Rose Bengal score was >4. The patient's ocular symptoms were managed with Hypromellose eye drops. A salivary scintiscan was undertaken which showed poor tracer uptake and secretion by the submandibular glands; overall this was suggestive of impaired salivary gland function. After discussion with the patient concerning management options, a decision was made to commence immunosuppressive therapy with ciclosporin 75 mg twice daily. The patient's renal function tests have been closely monitored and remained within normal limits. Follow up scintiscans at yearly intervals have shown no deterioration in salivary gland function. Recent scintigraphy 5 years after the birth of this lady's first child showed slight improvement in submandibular function and the patient continues to report no xerostomia.

Discussion

Congenital heart block occurs in approximately 1 in 20 000 births with a 10% neonatal mortality rate (Michaelson and Engle, 1972). It is defined as heart block existing at or dating from birth and is most commonly an isolated finding in a structurally normal heart of an otherwise healthy baby (Julkunen and Eronen, 2001).

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Isolated heart block detected after the newborn period has been associated with myocarditis, rheumatic heart disease, cardiac tumour, Lyme's disease, Marfan's syndrome and Ehlers–Danlos syndrome (Julkunen and Eronen, 2001). It may also be associated with autoimmune disorders such as 1°SS, systemic lupus erythematosus (SLE), 1°SS/SLE overlap syndrome and subacute cutaneous lupus erythematosus (Borda *et al*, 1996).

A Finnish study reported the long term outcome of mothers of children with isolated heart block and 58% of mothers of children with CHB had developed a definitive autoimmune disease by a mean of 10 years after delivery. Primary SS, either definite or subclinical, was the predominant autoimmune disease in this defined population (Julkunen and Eronen, 2001). The risk of succeeding pregnancies being affected by CHB has been reported as being up to 16% (Theander *et al*, 2001).

It has been known since the 1970s that there is a strong correlation between mothers whose maternal sera is SSA/Ro and SSB/La positive and children born with CHB (McCue *et al*, 1977). Although the molecular biology of the candidate antigens is well understood the arrhythmogenic and electrophysiological effects on the foetal heart are presently unknown. Available autopsies from infants affected with CHB have indicated there are no major structural defects in the heart but there is fibrosis of the atrioventricular (AV) node (Ho *et al*, 1986). These findings have lead to speculation that CHB may be the result of immune mediated tissue damage to the foetal heart following the transplacental passage of maternal SSA/Ro and SSB/La autoantibodies. However, it is unclear how the SSA/Ro and SSB/La antigens, which are normally sequestered within the confines of the cell nucleus and cytoplasm, become accessible to the immune response. One possible mechanism has been highlighted by data from recent work demonstrating that SSA/Ro and SSB/La antigens are present on apoptotic blebs, on the surface of the actively remodelling foetal cardiocytes (Miranda *et al*, 1998). Once opsonized by SSA/Ro and SSB/La antibodies these apoptotic cardiocytes are able to activate macrophages *in vitro* (Miranda-Carus *et al*, 2000).

The recent development of animal models of CHB and the use of electrophysiological techniques has provided for alternative mechanisms that could be responsible for CHB (Boutjdir *et al*, 1997; Miranda-Carus *et al*, 1998; Mazel *et al*, 1999; Xiao *et al*, 2001). With these techniques it has been possible to demonstrate that affinity-purified SSA/Ro antibodies, from mothers whose children have CHB, induce complete AV node block in perfused human foetal heart preparations (Boutjdir *et al*, 1997). Furthermore, immunisation of female mice with recombinant SSA/Ro protein generated high-titre antibodies that crossed the placenta during pregnancy and were associated with AV node conduction abnormalities in a high proportion of the pups (Boutjdir *et al*, 1997; Miranda-Carus *et al*, 1998; Mazel *et al*, 1999).

Electrophysiological techniques have identified that the site of action of SSA/Ro and SSB/La antibodies may be the α_1-subunit of the L-type calcium channel (Xiao *et al*, 2001). The L-type calcium channels are widespread in the cardiovascular system and are critical for the propagation of an action potential in the AV node, as well as excitation coupling in the heart. As in foetal heart cells it is known that the L-type calcium channels density is lower (Hoerter and Vassort, 1982), this mechanism of SSA/Ro and SSB/La antibody action may provide an explanation as to why the foetal heart is effected by CHB while the maternal heart is unaffected.

Although the data are compelling, in that they suggest that SSA/Ro antibodies are pathogenic, they do not explain why only 2% of pregnancies from SSA/Ro positive mothers result in CHB (Brucato *et al*, 2001). Several possibilities have been suggested (Gordon *et al*, 2001): (1) a foetal event occurs making the foetal heart more susceptible, (2) CHB may be the result of another antibody, or (3) the majority of cases of CHB are subclinical.

Foetal event

Increased susceptibility of the foetal heart has been mentioned above and could occur because of increased apoptotic remodelling of foetal cardiocytes and/or as a result of differing densities of L-type calcium channels in the foetal heart.

Non-SSA/Ro antibody

In addition to SSA/Ro and SSB/La autoantibodies antibodies against muscarinic type-1 receptors (M1R) have been described in the maternal blood (Borda *et al*, 1999; Borda and Sterin-Borda, 2001). It has been suggested that as foetal heart expresses M1R while adult heart predominantly expresses M2R, anti-M1R antibodies would preferentially affect foetal heart (Borda *et al*, 1999).

A further antibody that has been implicated in CHB is a maternal antibody against endogenous retrovirus-3 (ERV-3) (Li *et al*, 1996). ERV-3 is expressed in foetal heart and antibodies from mothers who had children born with CHB showed the highest antibody titres (Li *et al*, 1996).

Majority of CHB cases are subclinical

It has been suggested that even clinically significant cardiac conduction disease may not be apparent at birth, and therefore the diagnosis of CHB be missed (Gordon *et al*, 2001). A case has been described in which a child from a mother with Sjögrens syndrome had a normal ECG at birth and did not present with mild CHB until the age of 2 years (Gordon *et al*, 2001); however, the child remained asymptomatic.

Conclusion

The mechanism underlying the association between 1°SS and CHB has yet to be elucidated and a number of theories have been postulated, which are not mutually exclusive.

Primary Sjögren's Syndrome should be considered in the differential diagnosis of a mother, whose child is born with CHB.

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