

Materno-fetal transmission of autoimmune disease

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1. Introduction

Most autoimmune diseases are characterised by the presence of circulating antibodies. While some, such as lupus, demonstrate a wide variety of antibodies (over 100 separate antigen–antibody systems have been reported in lupus), in others, there is seemingly a single ‘marker’ antibody. In some situations, the association between specific antibody and clinical expression is so restricted as to suggest a “cause and effect” relationship.

For example, mixed connective tissue disease, with its tendency to severe Raynauds phenomenon, is extremely interesting in that a significant percentage of the immunoglobulin circulating in these patients is antibody, directed against RNP.

Some of these unique relationships are listed in [Table 1](#).

Yet despite the closeness of the clinical associations, evidence of materno-fetal transmission of these antibodies and resultant disease has been lacking—with the notable exception of anti-Ro and congenital heart block.

In this review, I have selected two antibody-disease links—anti-Ro with neonatal lupus, and the hugely important association of thrombosis with antiphospholipid (aPL) antibodies.

2. Anti-Ro and heart block

Occasionally, offspring of mothers carrying anti-Ro antibodies develop skin rashes. These rashes often bear close similarities to the characteristic adult subacute cutaneous lupus erythematosus (SLE) rash, so characteristic of some anti-Ro positive lupus patients. The rash is transient, its presence coinciding with the presence of maternal anti-Ro antibodies in the offspring.

More serious in the offspring, and potentially life-threatening, is congenital complete heart block (CCHB). Offspring of women with anti-Ro antibodies have an approximately 2% risk of developing CCHB in utero. The target antigens of the anti-Ro antibodies have been cloned and identified as three proteins—52 KD Ro, 50 KD Ro and 48 KD La.

The reasons for the heart block (and more importantly the absence of heart lesions in the majority of babies) remain unclear. However, histologically, there is fibrosis of cardiac conduction tissue, and in some, a more widespread myositis. An animal model with mice actively immunised with Ro antigens has given insights, with pups born with a variety of conduction defects. It is likely that early inflammation and late fibrosis in the atrio-ventricular mode is involved.

The spectrum of disease is wide and varies from subclinical arrhythmia to severe cardiac impairment and death [\[1\]](#).

An intriguing possibility is that more subtle conduction defects in offspring of anti-Ro positive mothers may lead to sudden death (“cot death” or sudden infant death syndrome). The author forwards this as a hypothesis based on a single observation of a family with one child with diagnosed CCHB and another with “cot death”. It seems likely that fetal heart block is only the tip of the iceberg in this neonatal syndrome.

3. Antiphospholipid syndrome (APS: Hughes syndrome)

3.1. Background

Twenty years ago, in 1983, we described a syndrome consisting of thrombosis, recurrent miscarriage, neurological disease and (occasional) thrombocytopenia, associated with the presence of circulating antiphospholipid antibodies [\[2,3\]](#). This syndrome originally seen in our lupus patients, but, more importantly, frequently seen in the absence of other autoimmune diseases, is important for three reasons:

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Table 1
Antibodies and diseases

Antibody	Clinical feature
Anti-Ro	Congenital heart block
Antiphospholipid (aPL)	Thrombosis
Anti-RNP	Mixed connective tissue disease
Anti-Jo-1 (and other anti-tRNA synthetases)	Myositis
Anti-mitochondrial	Biliary cirrhosis
Anti-centromere	CREST

First, it (almost uniquely) results in both arterial *and* venous thrombosis.

Second, it is easily recognisable, and prophylactic therapy (anticoagulation) is available.

Third, it may well come to be recognised as the most common major autoimmune disease—a condition with ramifications for the whole of medicine.

3.2. Clinical features

The central feature is thrombosis—both venous and arterial. Venous thrombosis may be ‘idiopathic’ or follow known risk factors such as pregnancy, smoking, the oral contraception pill, or long haul flights (the “economy class syndrome”). Arterial thrombosis can affect any organ, notably the brain [4].

3.3. Brain

The most common clinical features are ‘neurological’. Headaches and migraine (often starting in teenage years) are an important feature. Other neurological features are strokes and TIAs, vertigo, memory loss (Alzheimer’s) and diplopia. Not surprisingly, a number of patients with Hughes syndrome are initially diagnosed as having multiple sclerosis [5].

3.4. Pregnancy

Thrombosis of the placenta is thought to be the main reason for recurrent pregnancy loss. Hughes syndrome is now said to be the most common *treatable* cause of recurrent pregnancy loss. The loss can occur at any stage of pregnancy and two or more *late* pregnancy losses are almost diagnostic of Hughes syndrome [6]. At the other end of the pregnancy spectrum, recurrent *very early* pregnancy loss may result in a diagnosis of infertility.

3.5. Pathogenesis

The potential reasons for the very close association between aPL and thrombosis are many—evidence for direct

antibody effects on endothelium, platelets and clotting proteins is documented.

Regarding materno-fetal transmission of disease, the evidence is slim—while thrombocytopenia and haemolytic anaemia in the offspring have been described, neonatal thrombosis is not a feature.

3.6. Implications of APS

Treatment with anticoagulation—aspirin, heparin or warfarin, is transforming the outlook for patients with Hughes syndrome. The implications are considerable: current published figures suggest a “1 in 5 rule of thumb” association with antiphospholipid antibodies:

- 1 in 5 young strokes (under 45)
- 1 in 5 DVTs
- 1 in 5 recurrent pregnancy losses
- 1 in 5 lupus patients

The impact of this treatable autoimmune disease on medicine and on health economics is considerable.

4. Conclusions

Autoimmune diseases are characterised by genetically determined abnormalities of the cellular and humoral immune systems. The presence of antibodies, while valuable diagnostically, has rarely equated directly to disease pathogenesis. One notable exception may be anti-Ro antibodies and the production of congenital heart block.

Another potentially important association may be the link between antiphospholipid antibodies and APS or Hughes syndrome.

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