

REVIEW FOR THE PRIMARY CARE PHYSICIAN

Neonatal rheumatic diseases

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INTRODUCTION

Rheumatic diseases are rarely encountered in newborns and fall broadly into three groups: (a) transplacentally acquired immunological diseases such as neonatal lupus and neonatal antiphospholipid syndrome; (b) genetic conditions such as the chronic infantile neurologic cutaneous and articular (CINCA) syndrome (also known as neonatal-onset multisystem inflammatory disease - NOMID); and, (c) other miscellaneous disorders that may rarely present in neonatal period such as Kawasaki disease, Behçet's disease and systemic-onset type of juvenile idiopathic arthritis (JIA).

Neonatal lupus and neonatal antiphospholipid syndrome are considered *in vivo* models of passively acquired autoimmune diseases, which result from the transplacental passage of specific maternal autoantibodies [1-3]. There are many maternally derived autoantibodies which are capable of binding to fetal antigens, but only a few bring about neonatal illness. The most prominent fetal or neonatal effects are observed in transplacental passage of autoantibodies that have a causative role in the pathogenesis of autoimmune disease. Transport of maternal autoantibodies across the placenta is a selective process that begins at about 12 weeks of gestation and accelerates after 22 weeks of gestation. The bulk of transferred autoantibodies belong to the subclasses IgG₁/IgG₃, and the time course of clinical symptomatology often parallels the presumed half life of IgG immunoglobulins. Conversely, if autoantibodies are demonstrable in the neonate in the absence of clinical effects, they may only be an epiphenomenon of the maternal disease.

CINCA syndrome is a member of the rapidly expanding family of autoinflammatory disorders characterized by self-resolving attacks of fever accompanied by somewhat specific clinical features [4]. These disorders have been extensively characterized recently, with a growing identification of genes involved in the pathogenesis.

This review focuses on recent advances relevant to primary-care physicians in the understanding of neonatal rheumatic diseases. The clinical features and possible pathogenic mechanisms of these diseases are described, with particular emphasis on their early clinical recognition. The literature search engines included PubMed, MEDLINE and Science Citation Index. The relevant articles were also identified by searching the references of available meta-analyses and review articles, and bibliography of pertinent references.

NEONATAL LUPUS

Neonatal lupus is a rare disease of the developing fetus and neonate acquired from the transplacental passage of specific maternal autoantibodies, in particular those directed against the extractable nuclear antigens Ro (also called SSA) and La (also called SSB) [1, 2]. Anti-Ro/La antibodies are present in a high percentage of patients with systemic lupus erythematosus (SLE) and Sjögren's syndrome, but mothers with a known connective tissue

disease and positive anti-Ro/La antibodies have only about 1-5% risk of delivering a child with neonatal lupus [5, 6]. On the other hand, neonatal lupus can be seen in the offspring of mothers who do not have any signs or symptoms of a connective tissue disorder, and the first demonstration of anti-Ro/La antibodies in these mothers occurs during the pregnancy or after delivery of an affected child.

Clinical features

The clinical features most clearly associated with neonatal lupus include cardiac disease, skin disease, hepatobiliary disease and cytopenia. The noncardiac manifestations of neonatal lupus are generally transient, resolving by 6 months of life coincident with the disappearance of maternal autoantibodies from the infant's circulation. The most frequent lesion of cardiac neonatal lupus is complete (i.e., third degree) heart block, which is almost always permanent.

The classic presentation of neonatal lupus is one of a fetus or newborn discovered to have a slow heart rate due to congenital heart block in the absence of a structural heart disease. Many cases are discovered *in utero*, most commonly between 18 and 24 weeks of gestation [7]. The identification of fetal bradycardia (i.e., heart rate less than 120 per minute) by either auscultation or routine obstetric ultrasound requires that the mother be referred for immediate fetal echocardiography to confirm the presence of heart block and to document the degree of the block. Autoimmune-associated congenital heart block can be first, second, or third degree, and may or may not be progressive after detection *in utero* or postnatally [8]. Only second or third degree heart block is clinically manifested as bradycardia. It is estimated that up to one third of pregnancies complicated by fetal complete heart block result in intrauterine death, which is usually related to intractable heart failure and development of *hydrops fetalis*. Besides congenital heart block, other cardiac manifestations have been reported, such as myocarditis, dilated cardiomyopathy, sinus bradycardia, QT interval prolongation and, rarely, structural heart defects [9, 10].

The skin rash of neonatal lupus characteristically appears a few days or weeks after birth, particularly after sun exposure. It consists of annular ([Figure 1](#) and [Figure 2](#)) or elliptical erythematous plaques ([Figure 3](#)) most often located on the scalp, face and extremities. Skin lesions are transient, lasting weeks to months; these usually resolve without scarring. Hypopigmentation is frequent and may be a prominent feature. Rarely, remnant telangiectasias can occur at previously affected sites [11]. The differential diagnosis of isolated cutaneous neonatal lupus includes tinea faciei, a photosensitive drug eruption, urticaria, seborrheic dermatitis and annular erythemas.

Hepatic dysfunction occurs in approximately 15% of cases with neonatal lupus and can present as severe liver failure *in utero* or after birth, transient cholestatic hepatitis and

transient elevations of aminotransferases. Hepatobiliary disease may occur as the sole clinical manifestation, but is commonly associated with other manifestations of neonatal lupus [12, 13].

Occasionally, newborns of mothers with anti-Ro/La antibodies may present with hematological manifestations including thrombocytopenia, anemia and neutropenia [14]. There have also been several case reports of various neurological manifestations associated with neonatal lupus [15, 16].

Pathogenesis

Presumably, the fetus develops normally until maternal IgG antibodies against the Ro and La proteins are actively transported across the placenta beginning at 12 weeks of gestation. Although the Ro and La proteins are normally intracellular and thus inaccessible to circulating antibodies, they are expressed on the developing fetal heart at different stages of gestation. It has been demonstrated that anti-Ro/La antibodies bind to fetal but not adult heart, and direct binding to fetal cardiac proteins may trigger an inflammatory response and cause tissue damage [17]. Despite exposure to the identical circulating autoantibodies, the maternal heart is never affected.

The exact pathogenetic mechanism of non-cardiac manifestations is still unknown, but it has been hypothesized that the timing of transplacental passage of maternal autoantibodies coincides with the period of maximal vulnerability of selected fetal organs [18].

Finally, it should be emphasized that specific maternal autoantibodies are probably necessary, but are not sufficient, for development of neonatal lupus. Several concomitant maternal, fetal or environmental risk factors may contribute to the pathogenesis of this disease.

Management

Prior to the development of fetal echocardiography, auscultatory evidence of regular bradycardia alerted the clinician to the congenital heart block, which could only be confirmed after birth. Fetal echocardiography is now used to establish the diagnosis of congenital heart block and it is recommended that the fetuses of all women with anti-Ro/La antibodies be evaluated by serial echocardiography. Echocardiograms are done weekly from 16 to 26 weeks and every other week until 32 weeks. A recent major advance in echocardiography was the development of a new non-invasive Doppler technique to measure the mechanical PR interval, which has made possible the *in utero* detection of first-degree heart block in the absence of an electrocardiogram. This technique allows earlier diagnosis and has paved the way for effective prenatal treatment in fetuses with incomplete heart block [19, 20].

The most common prenatal interventions attempted are systemic glucocorticosteroids and medications to treat heart failure. The rationale for treatment of identified heart block with glucocorticosteroids is to diminish the cardiac inflammatory injury and to lower the maternal autoimmune response. Dexamethasone, which is not metabolized by the placenta and is available to the fetus in an active form, is given at a dose of 4 mg/day. Fetal risks secondary to dexamethasone include oligohydramnios, intrauterine growth retardation and adrenal suppression. Sympathomimetics, diuretics and fetal pacing are reserved for those cases where the fetus is in a life-threatening situation with hydrops and deteriorating cardiac function [21, 22].

Postnatal treatment of the symptomatic infant with complete heart block is based on pacemaker implantation, and supportive treatment for low output or congestive heart failure.

Cutaneous manifestations of neonatal lupus generally do not require any treatment; however; topical application of a mild glucocorticosteroid cream may hasten the resolution of the lesions and be used for cosmetic reasons. All infants whose mothers have anti Ro/La antibodies should be protected from excessive exposure to the sun, which may induce or exacerbate skin lesions. In most cases, hepatobiliary and hematological manifestations are self-limited and the usual approach to management is reassurance to the parents and continued observation of the infant (including determination of titers for antinuclear antibodies and antibodies against extractable nuclear antigens, liver function tests, complete blood count and electrocardiogram) at least until transplacentally acquired autoantibodies become undetectable.

Prognosis

Nearly all children with complete heart block require implantation of a pacemaker at some point in their lives, frequently in the neonatal period [7]. Despite early pacing, complete heart block carries high neonatal morbidity and high mortality during the first 12 months of life [23].

If a mother has already had one child with congenital heart block, there is approximately a 15 to 20% risk of having another child with the same problem, supporting close fetal echocardiographic monitoring and considering therapeutic interventions [7].

Apart from cardiac disease, children with neonatal lupus grow and develop normally. They have only a slightly higher risk for developing autoimmune disease later in life attributable to the genetic predisposition [24, 25]. Parents of these infants should be counseled that the risk of their offspring developing autoimmune diseases is similar to the risk in children of women with SLE or another connective tissue disease.

NEONATAL ANTIPHOSPHOLIPID SYNDROME

Neonatal antiphospholipid syndrome (APS) is a rare clinical entity characterized by neonatal thrombotic disease [3]. Autoantibodies that have been causally associated with neonatal APS include antiphospholipid antibodies (aPL), namely the β_2 glycoprotein I - dependent anticardiolipin antibodies and lupus anticoagulants. These autoantibodies have a well-recognized pathogenic role in thrombotic diathesis and have been associated with a number of obstetric complications such as recurrent pregnancy loss, pre-eclampsia, fetal growth retardation and pre-term delivery [26]. While women with aPL show an unusually high incidence of pregnancy complications, the aPL-related thrombosis in their offspring seems to be exceedingly rare. The low frequency of neonatal thrombosis has been attributed to the lack of the most known "second hit" risk factors in infants (such as atherosclerosis, cigarette smoking, oral contraceptives etc.), and to a low transplacental passage of IgG2 subclass of aPL, which are responsible for most clinical pathogenicity [28, 29].

Neonatal thromboses associated with transplacentally acquired aPL were most commonly described in cerebral vessels and abdominal organs; however, vascular occlusion in APS may involve the arteries and veins at any level of the vascular tree and in all organ systems [3]. Special concern is needed particularly when dealing with aPL-positive infants who are exposed to other acquired thrombotic risk factors (i.e., central vascular catheters, sepsis, prematurity, congenital heart disease), and possibly inherited prothrombotic disorders (i.e., deficiencies of antithrombin III, protein C, protein S, factor V Leiden mutation). There have also been scattered reports of thrombotic events in the fetuses of aPL-positive women, resulting from intra-uterine exposure to aPL [30, 31].

Both aPL and anti-Ro/La antibodies may be simultaneously present in a woman with connective tissue disease making the distinction between neonatal lupus and neonatal APS sometimes difficult [32, 33]. In fact, some of the hematological and neurological manifestations reported in neonatal lupus could be related to the presence of aPL [34, 35]. At the present time, however, the exact clinical criteria for these clinical entities are not available.

CHRONIC INFANTILE NEUROLOGIC CUTANEOUS AND ARTICULAR (CINCA) SYNDROME

CINCA syndrome is a rare congenital inflammatory disease characterized by a triad of cutaneous rash, chronic meningitis and arthropathy [36-38]. The gene defective in CINCA syndrome (CIAS1 gene; so named for *cold-induced autoinflammatory syndrome*) was identified by positional cloning and encodes a 920-amino acid protein cryopyrin, which is involved in the regulation of apoptosis [39, 40]. The CIAS1 gene is also the site of mutations causing two other autoinflammatory disorders, Muckle-Wells syndrome and familial cold autoinflammatory syndrome [41]. Several distinct mutations have been identified in CIAS1

gene, but there is no apparent clustering of mutations associated with particular illness. Because of clinical similarities between these syndromes and the same apparent genetic basis, it has been proposed that they represent a spectrum of disease, with familial cold autoinflammatory syndrome the mildest and CINCA syndrome the most severe. Mutations in CIAS1 gene were only identified in approximately half of the patients with CINCA syndrome, which raises the possibility of genetic heterogeneity [40].

The most striking feature of CINCA syndrome is the onset in the neonatal period. Persistent and migratory urticarial rash is often present at birth or develops within the first weeks of life. It can be confused with a systemic JIA rash, but is more pronounced and present for the life of the patient [42]. The joint manifestations usually begin in the first year of life and most commonly involve knees, ankles, elbows, wrists, hands and feet. They could be limited to mild arthritis during flare-ups or present with severe deforming arthropathy with typical radiographic changes [43, 44]. Joint enlargement in CINCA syndrome is described as hard and bony with deformities from epiphyseal and growth cartilage overgrowth, rather than the soft tissue and synovial proliferation seen in JIA. The most distinctive changes occur in the metaphyses and epiphyses of the femur, radius and tibia, resulting in premature growth plate closure and shortened long bones. A premature patellar ossification is frequent with a subsequent overgrowth of the patella. Neurological impairment results from chronic meningeal inflammation and is characterized by symptoms indicating meningeal irritation (i.e., headaches, vomiting, seizures, spastic diplegia) and progressive cognitive impairment. Significant sensory abnormalities including ocular manifestations, perceptive deafness and hoarseness commonly occur in older patients. In the worst cases, eye involvement can lead to a progressive visual defect and sometimes to blindness [45]. Distinctive morphological features with frontal bossing, hypoplastic midface, shortening of distal limbs with clubbing of the fingers and growth retardation have been described.

Laboratory investigations reveal iron-resistant hypochromic anemia, leukocytosis with neutrophilia and eosinophilia, high platelet counts, elevated erythrocyte sedimentation rate and polyclonal hypergammaglobulinemia. There are usually no autoantibodies or antigen-specific T-cells.

The course is one of a chronic, persistent inflammatory disease with numerous flare-ups associating fever, hepatosplenomegaly and lymphadenopathy. Significant musculoskeletal functional disabilities occur in more than 50% of those affected, and severe failure to thrive and short stature are present in virtually all patients. Progressive neurological involvement with consequent developmental delay can occur with time. The mainstay of current therapy for CINCA syndrome consists of symptomatic relief with the use of nonsteroidal anti-inflammatory drugs and glucocorticosteroids. Patients may also benefit from

physiotherapy, splinting and occupational therapy. No therapeutic approach has been effective in altering the course of the disease.

OTHER DISORDERS

Kawasaki disease

Kawasaki disease is rarely encountered in the neonatal period. Of the 105,755 patients with Kawasaki disease included in the Japanese database over 25 years, only six were neonates [46]. The rarity of disease in neonates has been explained by the protective effects of the transplacentally transferred maternal IgG immunoglobulins. Alternatively, the rare incidence rate at this age may be explained by infection theory, since neonates usually stay at home and seldom have chance to be exposed to the infectious agents. The reported neonatal cases had a rapid and severe course, and usually presented with atypical clinical features. In particular, they had a higher incidence of cardiac complications and usually did not fulfill the established diagnostic criteria of Kawasaki disease [47, 48].

Behçet's disease

A transient form of Behçet's disease may develop in a neonate of a mother with this disease. In all reported neonatal cases, mothers had oral and genital ulceration during the pregnancy [49-53]. The condition is thought to be transmitted by an immune mechanism similar to the mechanism of neonatal lupus; however, the causative autoantibodies for neonatal Behçet's disease have not been identified. The most common features of neonatal Behçet's disease include fever, orogenital ulcerations, pustulonecrotic skin lesions, bloody diarrhea, stridor and intrauterine growth retardation. A case of transient neonatal Behçet's disease with life-threatening complications has also been reported. This baby developed pyrexia, blood-streaked diarrhea, vasculitic skin lesions and recurrent oral and pharyngeal ulcers, resulting in progressive inspiratory stridor and respiratory arrest [53]. Clinical manifestations of neonatal Behçet's disease usually develop within 1 week of birth and resolve by the age of 8 weeks, supporting the hypothesis that the disease is caused by the transplacental passage of maternal antibodies. Healing of the severe ulceration may result in extensive scarring and therapeutic intervention with glucocorticosteroids is recommended after diagnosis. Before applying this treatment, a disseminated infection (e.g. herpesvirus, *Staphylococcus*) must be excluded.

Polyarteritis nodosa and other rare vasculitides

Vasculitis in a neonate born to a mother with vasculitis is a rare event and only few isolated cases have been described. At least three cases of neonatal vasculitis have been reported in infants born to mothers with cutaneous polyarteritis nodosa [54-56]. During the

neonatal period these infants developed cutaneous vasculitis manifested by livedo reticularis, cutaneous nodules and acral necrosis. In all the cases, the vasculitis was confined to early infancy, suggesting that the disease was caused by a maternal factor that crossed the placenta.

Systemic juvenile idiopathic arthritis (JIA)

Neonatal onset of systemic JIA (Still's disease) is exceedingly rare, but needs to be considered in the differential diagnosis of a neonatal rash associated with systemic inflammatory signs [57, 58]. A neonate with evanescent rash that appeared on the second day of life in association with fever has been reported [58]. Over the first weeks of life, the infant developed lymphadenopathy and hepatosplenomegaly. At 15 months he presented with arthritis of the right knee joint, confirming the diagnosis of systemic JIA.

Other miscellaneous disorders

A number of other unrelated disorders may present in the neonatal period and should be considered in the differential diagnosis. They include hyper-IgD syndrome, acute febrile neutrophilic dermatosis (Sweet's syndrome), histiocytosis, mastocytosis, neonatal infections, as well as selected metabolic diseases and primary immunodeficiencies in which autoimmune disorders may occur [59].

SUMMARY

A variegated group of rheumatic disorders may occur in neonates. These disorders fall broadly into three groups: (i) transplacentally acquired immunological diseases such as neonatal lupus and neonatal antiphospholipid syndrome, (ii) genetic conditions such as the chronic infantile neurologic cutaneous and articular (CINCA) syndrome, and (iii) other miscellaneous disorders such as Kawasaki disease, Behçet's disease and systemic JIA that may rarely present in neonatal period. Those fetuses and infants at greatest risk for transplacentally acquired disease due to the maternal rheumatic disease should be under close observation in order to anticipate perinatal problems and to take prompt preventive and therapeutic measures. Early recognition and referral to the pediatric rheumatologist is important for effective management of neonates and could help avoid the possible serious complications of these diseases. In addition, appropriate counseling of the parents and family of the affected neonate is necessary in transplacentally acquired and genetic diseases.

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