Congenital complete atrioventricular block in the early pediatric population

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ABSTRACT: Congenital complete atrioventricular block (CCAVB) is a rare potentially lethal disease with an estimated incidence of 1 every 15.000 to 20.000 live born infants.

In structurally normal hearts two kinds of congenital heart block can be identified: one usually diagnosed in utero associated with the circulating maternal anti-SS-A/Ro and anti-SS-B/La antibodies, the other kind is detected later in the neonatal period or during the infancy or childhood and present no clear relation with maternal antibodies. Nowadays, the diagnosis can be made in utero as early as between week 16 and 28 of gestation by foetal echocardiography.

The mortality in isolated CCAVB is estimated between 8 and 16% and between 4 and 8% in children and adults. The mortality and morbidity of patients diagnosed outside the neonatal period is significantly lower than those with a in utero diagnosis.

Risk factors for worse outcome in CCAVB are the foetal diagnosis, the presence of hydrops fetalis, delivery at   32 weeks gestation, and a ventricular rate <55 beats/min in early pregnancy (13,18).

Aim of this review is to delineate the current knowledge on CCAVB presenting in children without structural heart disease including aetiology, outcome and management. Also outlined in this review are some of the problems still debated in this issue. (Heart International 2006; 2: 1-5)

KEY WORDS: Congenital complete heart block, Fetal heart block, Pacing, Anti-SS-A/Ro and anti-SS-B/La antibodies

INTRODUCTION

Congenital complete atrioventricular block (CCAVB) is a rare, potentially lethal disease with an estimated incidence of 1 every 15,000 to 20,000 live births (1). A recent comparative study conducted in Finland demonstrated an increasing incidence from 1 to 25,000 to 1 to 11,000 during the last decades; possible explanations are the enhanced neonatal care and also that the better diagnostic methods allow more antenatal diagnosis, and moreover, the increasing number of mothers with connective tissue disease with successful delivery (2).

Nowadays, the diagnosis can be made *in utero* as early as between week 16 and 28 of gestation by fetal echocardiography. Aim of this review is to delineate the current knowledge on CCAVB presenting in children without structural heart disease: etiology, outcome, management and which are still the open problems.

Aetiology and outcome

There are two kinds of congenital heart block in structurally normal hearts: the first one is usually diagnosed *in utero* and is associated with the circulating maternal anti-Sjögren Syndrome A and anti-Sjögren Syndrome B antibodies (anti-SS-A/Ro and anti-SS-B/La ribonucleoproteins antibodies) (3-5). The other kind of CCAVB is detected later in the neonatal period or during infancy or childhood, and there is no clear association with maternal antibodies as in the first kind (4, 6).

The first demonstration of a correlation between maternal systemic lupus erythematosus (SLE) and CCAVB was described in 1977 (7); subsequently the association between the presence of maternal anti SS-A/Ro and anti SS-B/La and the development of a CCAVB was confirmed and tested in many series (6,8). The pathological changes have been strictly correlated to the presence of circulating Anti SS-A/Ro alone or in conjunction with Anti SS-B/La even in mothers without clinical manifestations of connective disease (SLE, Sjögren's syndrome, rheumatoid arthritis, mixed connective disease). The signature histologic pattern of autoimmune CCAVB is fibrous replacement of the conducting tissue and, sometimes, of the surrounding myocardium, but also a fibroelastosis replacement and widespread dystrophic calcifications in several areas have been reported (5, 9). The immuno-histology of hearts from fetuses/neonates with CCAVB demonstrated the presence of an exaggerated apoptosis and macrophage infiltrates resulting in a progressive scarring. The mechanisms by which maternal antibodies initiate and finally eventuate the fibrotic transformation are not clear (5); moreover, a recent report suggests that transplacental transfer of maternal cells during the pregnancy creates a state of microchimerism that may concur to the pathogenesis of cardiac injury in neonatal lupus. Associations between maternal HLA, not fetal HLA, and the CCAVB in the fetus, in presence of maternal immune disease, have been also described (10).

Third degree atrioventricular block seems irreversible, but the widespread use of fetal echocardiography also helps in diagnosis of first and second degree blocks *in utero*, opening a possibility of treatment. However, it seems that incomplete AV block progresses to complete block post-natally despite the clearance of maternal antibodies from neonatal circulation (3). Recent reports suggest a direct role of maternal autoantibodies in inhibition of inward current calcium channels, and the presence of sinus bradycardia (SB) was identified, in an animal model, as a potential marker in detection and prevention of CCAVB (11) confirming clinical data correlating SB in infants born with mothers seropositive to anti SSA/Ro (12).

The immunologic basis of CCAVB can explain the development of dilated cardiomyopathy despite pacing; it seems that in up to 15% of cases a myocarditis/endocarditis occurs post-natally even after ten years (13, 14).

Echocardiography allows the *in utero* diagnosis and follow-up of CCAVB. The fetus may remain asymptomatic adjusting its stroke volume in order to compensate the bradycardia or may develop cardiac failure and intrauterine hydrops (15).

The mortality in infants with isolated CCAVB is estimated between 8 and 16% and between 4 and 8% in children and adults (1, 16). The mortality and morbidity of patients diagnosed outside the neonatal period is significantly lower than those with an *in utero* diagnosis (mortality of 5% vs 19% at a mean follow-up age of 22 years); early infancy seems the period of greatest risk of death (17).

Risk factors for worse outcome in CCAVB are fetal diagnosis, the presence of hydrops fetalis, delivery at 32 weeks gestation, and a ventricular rate <55 beats/min in early pregnancy (13, 18). Fetal hydrops was associated with a fetal and neonatal mortality between 83 and 100% in various reports and the coexistence of hydrops and endocardial fibroelastosis strongly predicts a worse prognosis (18).

Up to 50% of asymptomatic patients during childhood will complain of symptoms in adulthood and 10% will die prematurely; they could have the fatal event during their first Adams-Stokes episode (19, 20). A mean daytime heart rate < 50 beats/min has been reported as a risk factor for sincope and sudden death; moreover frequent episodes of junctional exit block, flat junctional response or tachyarrhythmias were present in patients who developed worse outcome (21).

In one report of 102 patients with CCAVB only 11% of neonatal and 12% of childhood patients had not required a pacemaker implant by the age of 20 years (13). Another negative prognostic sign is the presence of a prolonged QTc that has been reported in 7-22% of patients with CCAVB (20). In a recent report the overall morbidity of patients who survived is 17%; the presence of a dilated cardiomyopathy concurs to a worse outcome with a mortality rate of 75% (17).

Management and therapeutic options

Usually, the *in utero* diagnosis comes from the echocardiographic recognition of fetal bradycardia observing the difference in atrioventricular valve opening or ventricular activity in comparison to a higher atrial

rate (22).

The diagnosis in infancy and in childhood is not easy; in infancy a symptomatic bradycardia can manifest with poor growth and development, sometimes with sleep disorders such as nightmares and the need for frequent naps, or just simply with a sedentary attitude.

Several studies report *in utero* therapy with sympathomimetics, digitalis and steroids (4, 23, 24) in order to increase the heart rate, to reduce with digitalis both the heart failure and hydrops despite the AV block and to reduce the circulating maternal antibodies with steroids. Digoxin seems safe and represents a therapeutic option if the fetus presents with cardiac failure (23). Even if β-sympathomimetics can cause myocardial ischemia and pulmonary edema and sometimes the dosages needed to increase fetal heart rate are not tolerated by the mothers, the administration of maternal salbutamol can be an option in case of severe fetal bradycardia (24). Some positive effects have been registrated in fetus with heart rate <55 beats/min with the maternal assumption of terbutaline every 4-6 hours (25, 26).

In a recent study the maternal assumption of corticosteroids was evaluated in presence of Anti SS-A/Ro, prior or after the 16th week of gestation: none of the neonates treated before the 16th week developed CCAVB compared to the 25% of neonates whose mothers were not treated or treated after the 16th week (27).

Nowadays, pacemaker (PM) implantation has a pivotal role in management and therapy of CCAVB; even if eventually the patients will receive a PM, timing of implant depends strongly on symptoms and sometimes it is still controversial (28, 29).

In neonates with isolated CCAVB, the implant of a PM is recommended with a heart rate lower than 55 beats/min or if heart failure develops (30).

A recent study (16) identified the following indications for PM therapy: syncope, heart failure, left ventricular dilation, mitral valve regurgitation, unstable escape rhythm, inappropriate sinus tachycardia, a prolonged QT interval, presence of ventricular arrhythmias and a daytime bradycardia (<55bpm) in infants. In this study the PM therapy reduces both morbidity and mortality in children with CCAVB with and without cardiac malformation when compared to natural history data.

In addition, a prophylactic pacemaker treatment could be recommended in adolescents and young adults with CCAVB who are asymptomatic to prevent Adams-Stokes attacks and sudden death (31).

When the pediatric cardiologists decide the timing of PM implantation they need to evaluate also many technical elements. In the last two decades PM therapy in children has considerably improved mainly due to new generation generators, that are smaller, and to better leads, but in any case the morbidity and the necessity of reoperation and lead extraction still remain (16, 28, 30). Nowadays, the trend is towards a surgical approach in neonates and in prematures, implanting epicardial leads and especially steroid-eluting epicardial leads that demonstrated a longer longevity and a better threshold. The transvenous approach seems safe in children of 4-5 years of age with weight >10-20 kg; in infants and smaller children the diameter of innominate vein and superior vena cava is too small and there is the risk of occlusion (19, 30). Some centers are evaluating the implant of new smaller leads also in little children from both internal jugular and subclavian venous approach (32).

The PM generator is usually positioned in the abdominal wall with the epicardial lead surgical approach, and in a subpectoralis pocket if the transvenous approach is preferred. A typical problem with children is the out-growth of leads as the children grow up: the lead length should always be redundant in order to allow the out-growth of leads. Some authors suggest that the best positioning for the ventricular lead seems in the right ventricular outflow tract, because in children the heart grows in the long axis more than in short axis (19).

In children older than 3 years of age the double lead PM implant with a DDD mode is becoming more common (17). The DDD mode should be preferred in patients with sinus node dysfunction and some authors suggest the DDD mode in order to maintain the AV synchrony (33) although no definite evidence supports a preference for DDD mode versus single pacing lead (17, 28). Single pacing lead systems are well tolerated in children where VVIR mode responds adequately to their physiological needs and the incidence of pacemaker syndrome is low (17, 19, 34).

The follow-up of children with congenital complete heart block should include a complete clinical and in-

strumental evaluation (ECG, Holter ECG monitoring and treadmill exercise test for heart rate and pauses evaluation, and echocardiogram in order to assess ventricular dimensions and function). As many authors suggest, the decision to implant a PM in an asymptomatic patient depends on the patient's lifestyle, body size and on relative PM indications; when an adolescent reaches adult body size the benefit of the pacemaker in prevention of sudden death overweighs the risks of the implantation so the problem is to decide the proper timing of the implant (16, 17, 19, 35).

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