



Review

A combination therapy protocol of plasmapheresis, intravenous immunoglobulins and betamethasone to treat anti-Ro/La-related congenital atrioventricular block. A case series and review of the literature



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ABSTRACT

Objectives: The aim of this report was to evaluate the efficacy and safety of a combined treatment protocol used to treat 2nd and 3rd degree anti-Ro/La-related congenital atrioventricular block (CAVB).

Methods: Six consecutive women diagnosed with 2nd degree (three cases) or 3rd degree block (three cases) between 2009 and 2011 referred to our outpatient clinic underwent a combination therapy protocol composed of weekly plasmapheresis, fortnightly 1 g/kg intravenous immunoglobulins (IVIg) and daily betamethasone (4 mg/day) throughout pregnancy. IVIg (1 g/kg) treatment in the neonates was begun at birth and administered every fifteen days until passive maternal antibodies became undetectable.

Results: The fetuses affected with 2nd degree block (cases 1, 2 and 3) reverted to a normal atrioventricular conduction after combined therapy, while those with a 3rd degree block remained stable (case 4), showed an increase in the ventricular rate (case 5) or an improvement in cardiac function (case 6). None of the fetuses with 3rd degree CAVB had other cardiac complications such as cardiomyopathy or fetal hydrops. The follow-up of the children affected with 2nd degree CAVB revealed a complete regression of the block in cases 1 and 3, and no signs of relevant worsening in case 2. The infants affected with 3rd degree block (cases 4, 5, and 6) remained stable and until now only one has required a pacemaker at the age of 10 months.

Conclusions: If these results are confirmed by large-scale studies, this protocol could lead to improved outcomes in the treatment of this devastating disease.

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Abbreviations: CAVB, congenital atrioventricular block; IVIg, intravenous immunoglobulins; ECG, electrocardiogram; IUGR, intrauterine growth restriction; EF, ejection fraction.

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1. Introduction

Neonatal lupus syndrome is a passively transferred autoimmune disease associated with transient cutaneous, hematologic, and hepatic abnormalities as well as permanent cardiac disorders [1–3].

Congenital atrioventricular block (CAVB) is the most frequent manifestation of neonatal lupus which is attributed to anti-Ro/SSA and/or anti-La/SSB-mediated inflammation and subsequent fibrosis of the atrioventricular node [4]. In prospective studies, the reported prevalence of fetal CAVB is 1–5%, which rises to 6–25% [5–7] for women with a previously affected child. Other cardiac complications such as myocarditis, pericardial effusions, fetal hydrops, endocardial fibroelastosis and dilated cardiomyopathy can complicate CAVB [8,9]. The perinatal mortality of neonates affected with CAVB is reported to approach 30% and increases when the disease is associated with endocardial fibroelastosis or cardiomyopathy [10]. Seventy percent of surviving infants require permanent pacemaker placement [10]. The first signs of CAVB are usually noted during the 18–24th weeks of gestation [11]. According to published data, it appears to be a progressively developing disease [12] although there have been frequent reports of fetal cardiac conduction returning to normal in

both treated and untreated fetuses with 1st degree CAVB [12,13]. Regression of a 2nd degree CAVB is still a debated phenomenon [12,14–16]. Third-degree or complete heart block seems to be permanent despite any type of treatment [15–17].

The main therapy generally employed for CAVB is fluorinated steroids, such as betamethasone or dexamethasone, which are only partially inactivated by the placental 11 beta-hydroxysteroid dehydrogenase complex, and thus have satisfactory bioavailability to the fetus. The rationale behind this treatment is to diminish the inflammatory component in the fetal conduction system and myocardium and, thus, to reduce cardiac injury. It does not reverse the third degree heart block and its effectiveness in reversing the block of second degree is not shown [15].

The number of alternative/additional therapies is limited and includes plasmapheresis [18] or intravenous immunoglobulins (IVIG) [19]. Plasmapheresis lowers the levels of anti-Ro/SSA and anti-La/SSB antibodies in maternal blood inhibiting their transplacental transfer and preventing the damage they cause to the fetal heart. Plasmapheresis has until now been taken into consideration mainly to prevent CAVB and there are some reports concerning its use in diagnosed mothers [20–26]. The procedure has, moreover, always been performed in conjunction with

Table 1
Studies assessing the use of plasmapheresis during pregnancy to treat CAVB.

Author/ year, (ref)	No. of patients	CAVB degree at detection	Medications	Outcome after treatment
Herreman et al. 1985 [21]	1	3rd	Plasmapheresis and prednisone	Unvaried, 3rd degree
Buyon et al. 1987 [24]	1	3rd	Plasmapheresis and dexamethasone	Improvement of myocarditis and pericarditis, 3rd degree
Arroyave et al. 1995 [22]	1	3rd	Plasmapheresis and prednisone	Intrauterine death
Saleeb et al. 1999 [25]	1	2nd/3rd	Plasmapheresis and fluorinated steroid	Transient regression to 1st/2nd degree, 3rd degree at birth
Zemlin et al. 2002 [23]	1	3rd	Plasmapheresis and dexamethasone	Unvaried, 3rd degree, perinatal death
Ruffatti et al. 2005 [26]	1	2nd	Plasmapheresis and dexamethasone	2nd degree/normal AV conduction, 2nd degree/sinus rhythm at birth
Ruffatti et al. 2012 [20]	2	2nd	Plasmapheresis, IVIG and betamethasone	Normal AV conduction, 1st degree at birth
		2nd	Plasmapheresis, IVIG and betamethasone	Normal AV conduction, 1st degree at birth

CAVB: congenital atrioventricular block.

AV: atrioventricular.

IVIG: intravenous immunoglobulins.

Table 2
Studies assessing the use of IVIG during pregnancy to treat CAVB.

Author/ year, (ref)	No of patients	CAVB degree at detection	Medications	Outcome after treatment
Friedman et al. 2010 [34]	1	Mobiz 1–2nd degree	1 cycle IVIG and dexamethasone	3rd degree
David et al. 2010 [36]	1	2nd/3rd	1 cycle IVIG	Predominant NSR and intermittent 2nd degree, 2nd/3rd degree at birth
Brucato et al. 2011 [37]	4	2nd/3rd	1 cycle IVIG and dexamethasone	Intrauterine death
		2nd/3rd	1 cycle IVIG and dexamethasone	Unvaried
		3rd	1 cycle IVIG and dexamethasone	Resolution of myocarditis, 3rd degree
		3rd	1 cycle IVIG and dexamethasone	Resolution of myocarditis, 3rd degree
Ruffatti et al. 2012 [20]	2	2nd	Plasmapheresis, IVIG and betamethasone	Normal AV conduction, 1st degree at birth
		2nd	Plasmapheresis, IVIG and betamethasone	Normal AV conduction, 1st degree at birth

IVIG: intravenous immunoglobulins.

CAVB: congenital atrioventricular block.

NSR: normal sinus rhythm.

AV: atrioventricular.

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