

● Case report and literature review

## PRENATALLY DETECTED NON-IMMUNE ATRIOVENTRICULAR BLOCK AND MATERNAL ARRHYTHMIA - CASE PRESENTATION AND LITERATURE REVIEW



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### Abstract

Our clinical report describes a rare finding of a prenatally-detected congenital atrioventricular (AVB) block without associated maternal antibodies, which progressed from 1st/2nd degree AVB to complete heart block during second half of pregnancy. Obstetrical ultrasound at 12th week did not reveal any abnormalities and prenatal echocardiography (due to VSD in a family member) at the 18th week of gestation detected 1st degree block, then bigeminy and bradycardia. Transplacental treatment with B-2-mimetics was introduced. The delivery was organized in a tertiary center and a pacemaker for the newborn baby was secured and implanted in 15th day of life. Currently the boy's condition is good and stable. Before therapy with B-2-mimetics the mother underwent echocardiography and ECG which revealed clinically silent structural and conduction heart abnormalities. Literature findings suggest that parents of children with non-immune congenital or childhood AVB are more likely to carry clinically silent conduction abnormalities than general population. Given the corresponding findings in the mother and her son, they should be good candidates for genetic testing.

**Key words:** non-immune AV block, prenatal diagnosis, maternal arrhythmia

### INTRODUCTION

Complete atrioventricular block (AVB) in children is a serious condition increasing the risk of sudden death and usually followed by pacemaker implantation. Most often it accompanies structural heart diseases, but can also develop as an isolated abnormality. Moreover, isolated AVBs diagnosed in utero, at birth or within the neonatal period (0-27 days after birth) are distinct clinically from those detected later in child's life and are associated with worse prognosis and increased risk of recurrence in future pregnancies. They are distinguished and labeled as congenital AVBs<sup>1</sup>.

Approximately, congenital AVB affects 1:15000-20000 newborns<sup>2,3</sup>. In most patients diagnosed before 6 months of age, the block is caused by maternal anti-Ro (SS-A) and anti-La (SS-B) IgG antibodies penetrating placental barrier, accumulating in fetal tissues and causing inflammation and heart fibrosis<sup>4,5</sup>.

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However, a fraction of patients develops AVB without presence of maternal antibodies. In this report we present a boy who developed a complete non-immune congenital AVB gradually in utero and whose mother presents abnormal heart anatomy coexistent with arrhythmia. We also review the available literature on clinical features of antibody-

negative childhood AVBs focusing on familial history and proposed genetic associations.

### CASE REPORT

A 23-year old woman reported to gynecologist in 12th week (hbd) of her first pregnancy for routine ultrasound, which revealed no abnormalities. At 13.4 hbd nuchal translucency (NT) was 2mm (within normal limits). Due to maternal medical history (her brother with ventricular septal defect) detailed echocardiography was performed in 18.2 hbd, which confirmed normal heart structure but revealed intermittent 2nd degree AVB 2:1. The mother was referred to the Department of Diagnoses and Prevention Fetal Malformations in Medical University of Lodz. Two days

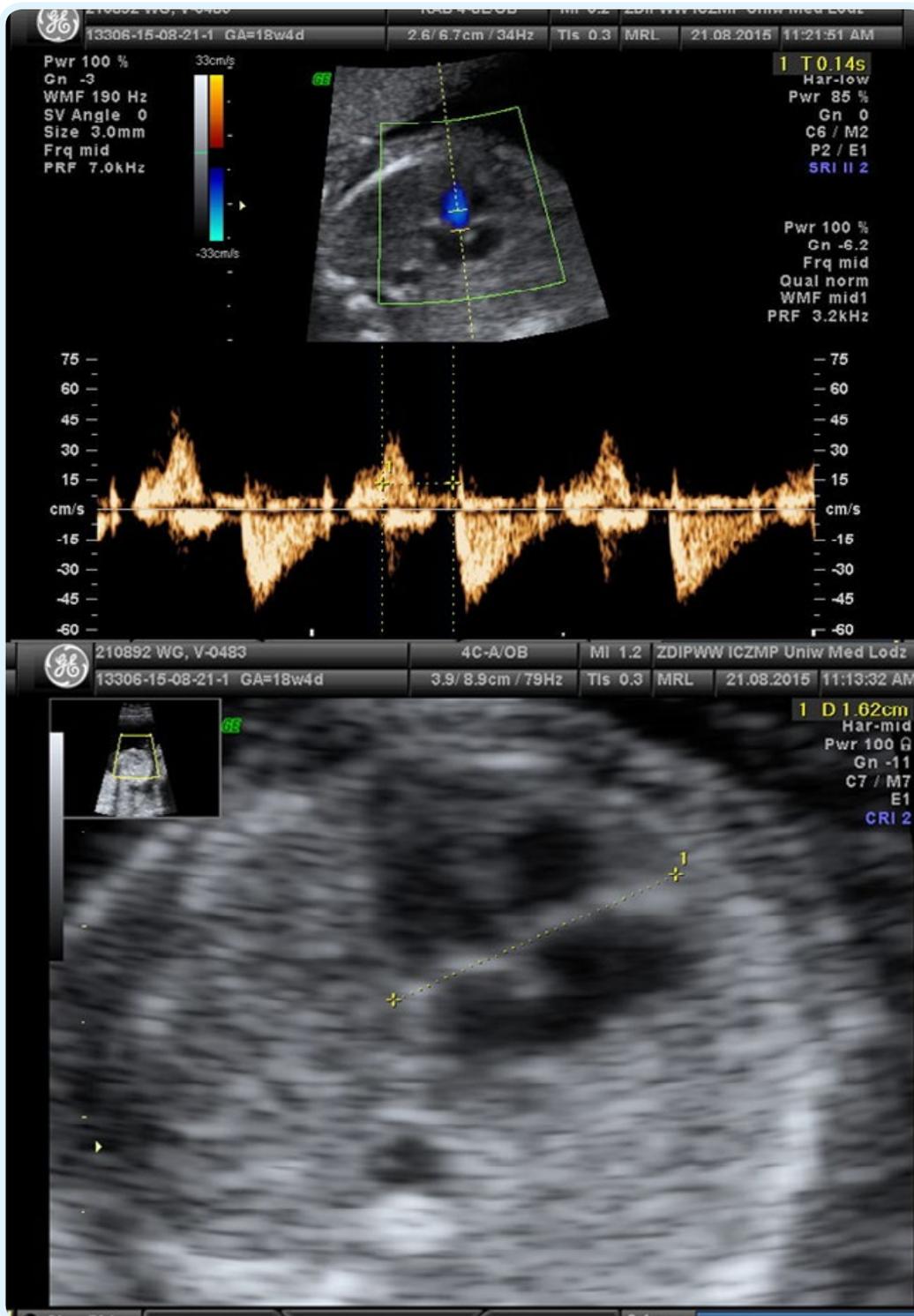


Fig. 1. Initial echocardiography in 18.4 hbd: sinus rhythm with prolonged PQ interval (140-150 ms). Normal heart anatomy.

later the arrhythmia was not detected (fetal heart rate 143/min, sinus rhythm), but PQ interval was elongated to 140-150ms, suggesting possible first-degree AVB (Fig. 1). The mother was tested for anti-Ro (SS-A) and anti-La (SS-B) IgG, rheumatoid factor and other antinuclear antibodies – all results were negative. In 32 hbd maternal B-2-mimetic (salbutamol) therapy was introduced to prevent fetal bradycardia. At 33rd week the fetus presented second-degree AVB with 2:1 ratio, temporarily reverting to sinus

rhythm and ventricular rhythm was 60-68/min (Fig 2A). In 38.4 hbd the block progressed to 3rd degree AVB with atrial rhythm 140-150/min and ventricular rhythm 45/min (Fig.2B)

The baby was delivered by CS at 39th week of gestation in our tertiary center with 3640g birth weight and scored 7/7/8 in Apgar scale. Due to neonatal bradycardia of 55-60/min orcyiprenalin infusion 0.5mg/day was administered, changed to 0.75 and later 1mg/day. In next days milrinon and steroids were added. In the 9th day the boy was transferred from neonatology clinic to the pediatric cardiology clinic (within the same hospital). Medication doses were adjusted due to variable clinical state of the newborn, who presented changeable 2nd/3rd degree AVB with sinus arrhythmias. Finally, the patient revealed a complete 3rd degree AVB with ventricular rhythm 52/min (Fig.3). On the 15th day of postnatal life the pacemaker (MICRONY II SR+) was implanted with successful VVI stimulation and without complications. A control holter ECG showed successful stimulation at 110/min.

During pregnancy, as maternal treatment with B-2-mimetics was suggested, the mother underwent a cardiac check-up: clinical exam, echocardiography and ECG. The echocardiography revealed unspecific, probably congenital heart anomaly with widened left ventricle especially in apex region and distorted wall contractility (Fig. 4A). ECG of the mother revealed left axis deviation with wide QRS, and negative T waves in V1-V6 (Fig. 4B).

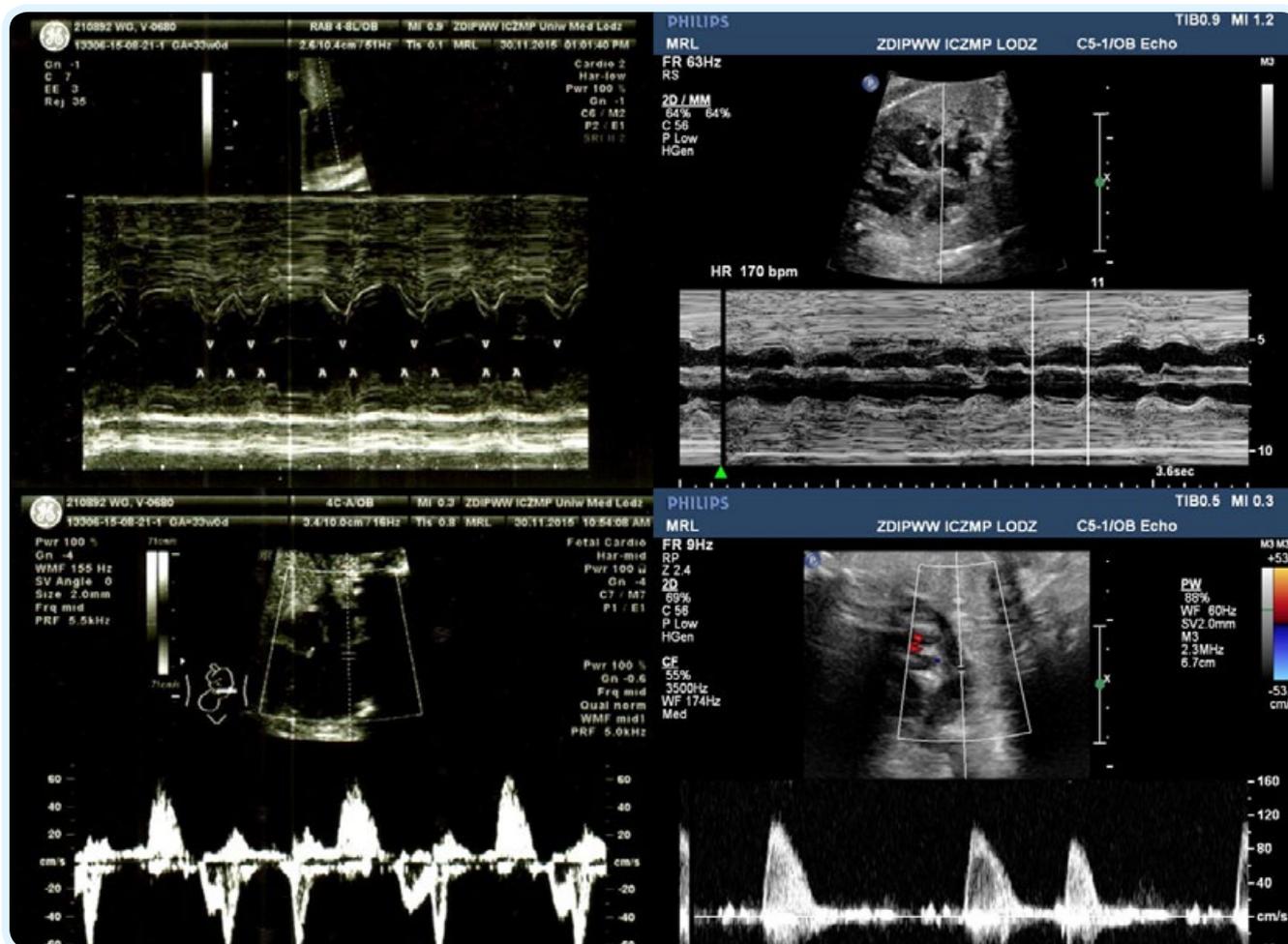


Fig. 2. Further prenatal findings. A: 33hbd. 2nd degree AVB 2:1, bradycardia. B: 38hbd, 3rd degree AVB, bradycardia

Prenatal findings				Postnatal findings		
13,4 hbd	18,2 hbd	18,4 hbd	33 hbd	38,4 hbd	1st-15th day	15th day
NT= 2mm	Intermittent 2nd degree AV block 2:1	Sinus rhythm, long PQ interval: 140-150 ms	2nd degree AV block 2:1, temporarily returning to sinus rhythm	3rd degree AV block	3rd degree AV block	Pacemaker implantation, successful VVI stimulation
FHR ??	Bradycardia	Normocardia	Bradycardia	Bradycardia	Bradycardia	Normocardia
Normal heart anatomy	Normal heart anatomy	Normal heart anatomy		Normal heart anatomy		Normal heart anatomy

Table 1.: Prenatal and postnatal findings in presented case.

The detailed summary of prenatal, postnatal and maternal findings in this case are presented in Table 1. and 2.

### DISCUSSION

Fetal complete heart block is a rare anomaly. According to the Polish Registry of Fetal Cardiac Anomalies<sup>6</sup>, in our country we recognize 2 to 13 fetal complete heart blocks per year (data from years 2004-2015, total number of complete heart blocks n=95, [http://www.orpkp.pl/index.php?LANG=pl&level=1&struct=1&start\\_page=1](http://www.orpkp.pl/index.php?LANG=pl&level=1&struct=1&start_page=1)). When detected in a fetus, it strongly indicates a pre-existing, sometimes subclinical, autoimmune condition in the

mother<sup>7</sup>. Therefore, all mothers of children with heart block detected prenatally should be screened for systemic lupus erythematosus and tested for associated antibodies. So far, all complete AVBs reported to the Registry were immune-mediated, which makes our case unique in the national scale.

We report a prenatally-detected non-immune congenital AVB with progression from 1st/2nd degree AVB to 3rd degree AVB before delivery. According to prenatal diagnosis, the therapy with B-2-mimetics was introduced early, the mother was scheduled for delivery in a referential hospital where the pacemaker implantation could be performed. This allowed for a safe



Fig 3. Maternal findings. A – echocardiography: dilated left ventricle and contractility disorders. B - ECG: left axis deviation with wide QRS, and negative T waves in V1-V6.

and cost-effective transport in-utero contrary to emergency transport after birth<sup>8</sup>. This proves that screening prenatal echocardiography brings important clinical information including those about rhythm abnormalities and should be performed at least once in a pregnancy.

In 2011 the Fetal Working Group of the European Association of Pediatric Cardiology analyzed the clinical course of isolated AVB in the fetus basing on 175 retrospectively cases<sup>9</sup>. They compared the outcomes among different lines of treatment including watchful observation, steroids and betamimetics. Their results do not support any specific therapeutic strategy. Specifically, transplacental steroid treatment had no effect on intrauterine or neonatal survival. Given the uncertain benefit of corticosteroids and non-immune character of AVB in our patient, only betamimetics were used in our case.

Interestingly, the AVB in the fetus coincided with cardiac structural and rhythm abnormalities in the mother and congenital heart defect in her brother. This, coupled with mother`s seronegativity, is an important indicator that heart pathologies observed in the family may have a genetic background.

Chang et al identified seven cases of non-immune second degree AVB detected in utero and analyzed their clinical course. The age of diagnosis ranged from 18 to 38 weeks<sup>10</sup>. In 6 patients the abnormality reverted to sinus rhythm before labor without later recurrence. The other AVB persisted over delivery and progressed to complete block. Contrary to literature search by Chang et al, the block in our patient progressed to complete AVB prenatally and not reverted after birth.

In 2014, Leszczyńska et al reported 5 cases of prenatally-diagnosed complete AVBs. Contrary to literature findings, in this group only one child had a seropositive mother<sup>11</sup>. In one non-immune case AVB coincided with complex heart abnormality.

Jaeggi et al reported their institution`s experience with 3rd degree isolated congenital AVB. Out of 102 cases of CAVB diagnosed pre- and postnatally, 5 were non-immune. Unfortunately, the numbers were insufficient to compare the clinical course of immune vs non-immune AVBs. However, the study showed that children diagnosed prenatally have higher risk of pacemaker implantation and repeat pacemaker-related interventions than those diagnosed after birth and prenatal cases can be associated with higher mortality<sup>12</sup>.

Villain et al. compared the AVBs by mother`s seropositivity. It turns out immune-mediated AVB were diagnosed mostly in utero, while non-immune after childbirth. Moreover, seronegative cases showed higher rate of progression from incomplete to complete block. On the other hand, they were associated with lower mortality<sup>13</sup>.

A large multicenter study by Baruteau et al. (141 non-immune isolated AVBs diagnosed either in utero or in early childhood) 26 cases fulfilled criteria of congenital AVB – 12

Maternal findings	
Clinical findings	None
ECG	Left axis deviation with wide QRS and negative T waves in V1-V6.
Echocardiography	Abnormal distension of left ventricle with wide apex

Table 2. Maternal findings during control ECG and echocardiography.

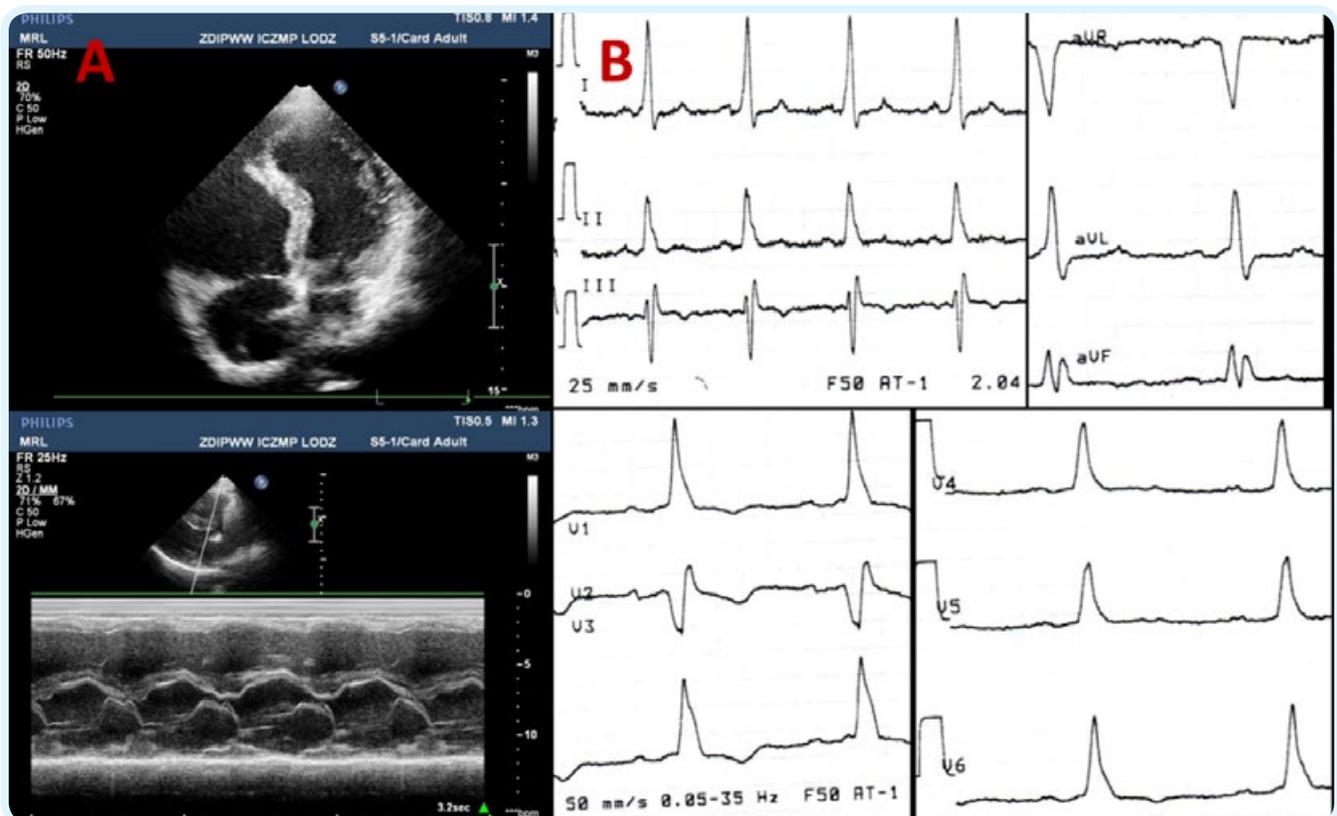


Fig 4. Maternal findings. A – echocardiography: dilated left ventricle and contractility disorders. B - ECG: left axis deviation with wide QRS, and negative T waves in V1-V6.

diagnosed in utero (mean hbd 36,8 +/- 2.1 weeks) and 14 at birth or in neonatal period. The group presented a variety in block severity and associated conduction disorders: 8 patients presented with incomplete AVB (4 with narrow QRS, 4 with wide QRS) and 18 with complete AVB (14 narrow QRS, 4 wide QRS).

Following their line of investigation, the team examined 130 parents of previously-analyzed children and compared them with matched healthy control. They reported extremely high rate of conduction abnormalities in parents (50.8%) compared with population-based control (5.6%)<sup>14</sup>. Most often occurring abnormalities were long PR interval, complete or incomplete block of right or left bundle branch.

This shows that idiopathic congenital and childhood AVB has a strong genetic factor, characterized by autosomal dominant inheritance with incomplete penetrance and variable expressivity. Genes with reported association with congenital heart block include NKX2.5, SCN5A and SCN1B coding for the homeobox protein Nkx-2.5, voltage gated sodium channel Nav1.5 and the auxiliary subunit B of the voltage-gated sodium channel<sup>15</sup>. However, when 97 children of initial cohort were scanned for mutations in SCN5A gene, only 2 patients had positive results.

In another study, a repeated screening of French cohort revealed nonsynonymous variants also in two patients, in NKX2.5 and SCN1B genes respectively<sup>15</sup>. The study also found 10 variants in TRPV4 gene in 14 patients and, after frequency evaluation, 5 non-polymorphic variants were subjected to functional analysis. Two of them were associated with gain, one with loss of function. TRPV4 is probably expressed in atrial myocardium and mouse sinoatrial node cells. Although no cause-effect conclusions were drawn, TRPV4 gene has been established as probably involved in pathogenesis of childhood and congenital AVBs.

So far, the genetic arrangement of our patients is still under investigation.

## CONCLUSIONS

1. Congenital AVB may not be associated with maternal antibodies and have other, non-immune background.
2. Non-immune congenital AVB should also be an indication for cardiologic examination of a child`s parents who can carry subclinical rhythm and structural heart abnormalities.
3. Families with non-immunological arrhythmias and additional findings in parents (even clinically silent) might be good candidates for genetic testing.

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## Division of work

**Maria Respondek-Liberska, Niwald Marek, Kukawczyńska Elżbieta all participated in diagnostic process and provided medical care for both mother and child. Arkadiusz Michalak and Marta Witczak prepared the manuscript and literature review. All authors revised the manuscript before submission.**

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**Compliance with Ethical Standards**

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