

Fetal/Neonatal Pericardial Effusion in Down's Syndrome: Case Report and Review of Literature

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Am J Perinatol Rep 2018;8:e301–e306.

Abstract

We report a preterm (35 ^{4/7} weeks) male neonate with Down's syndrome (DS) diagnosed with isolated pericardial effusion (PE) at 20 weeks of gestation. He was born by precipitous delivery, needed no resuscitation and presented within first 24 hours of life with respiratory distress, anemia due to feto-maternal bleed, hypotension, hepatomegaly, and coagulopathy. Postnatal echocardiography confirmed a 5 mm rim of PE without tamponade, normal cardiac structure, and function. He was stabilized with ventilation, packed red cell, fresh frozen plasma, inotropes (dopamine, dobutamine, and adrenaline), and steroid (hydrocortisone). Subsequent evaluation confirmed hypothyroidism, transient myeloproliferative disorder (TMD), hepatic failure due to fibrosis/cirrhosis with portal hypertension, and steroid sensitive hypotension on two occasions possibly due to adrenal insufficiency. PE completely resolved over 2 weeks. In view of progressively worsening liver failure with ascites and portal hypertension, the family opted for palliation. Literature review has been discussed regarding perinatal onset of PE in DS.

Keywords

- Down's syndrome
- hypothyroidism
- pericardial effusion
- steroid
- transient myeloproliferative disorder

Pericardial effusion (PE) is occasionally reported in children with Down's syndrome (DS) either in isolation¹ (isolated PE) or as part of hydrops.² It can be associated with congenital hypothyroidism³ and transient myeloproliferative disorder (TMD).⁴ The pathogenesis of PE in DS is unclear. We describe a case of antenatally detected isolated pericardial effusion in DS in association with TMD, liver failure, hypothyroidism, and hypotension due to possible adrenal insufficiency. We reviewed the literature to understand the underlying mechanism, demography, association, and natural course of PE.

Case Report

Antenatal morphology scan and fetal echocardiography in a 39-year-old G3P3 mother revealed isolated PE with structurally normal heart, first identified at 20 weeks of gestation. Subsequent amniocentesis confirmed DS (47,XY). A male neonate at 35 ^{4/7} weeks gestation, birth weight 1,880 g (< 10th centile) was vaginally born at home through precipitous labor, needed no resuscitation and was retrieved to a tertiary Neonatal Intensive Care Unit by ambulance at 40 minutes of age. Initial examination showed moderate respiratory distress with FiO₂ (fraction

received
July 26, 2018
accepted
September 5, 2018

DOI <https://doi.org/10.1055/s-0038-1675337>.
ISSN 2157-6998.

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of inspired oxygen) 0.3, pallor (Hb 83 g/L), normal cardiovascular examination with normal noninvasive blood pressure (60/32, mean: 45), massive hepatomegaly (6 cm below costal margin) in the background of phenotypic DS. There was no hydrops, ascites or splenomegaly. He was stabilized with mechanical ventilation and packed cell transfusion (10 mL/kg twice). His liver function and coagulation profile were deranged: alanine transaminase (ALT) 318 IU/L, aspartate transaminase (AST) 1,147 IU/L; total bilirubin 41 micromol/L, direct bilirubin 6 micromol/L; alkaline phosphatase 163 IU/L; gamma glutamyl transferase (GGT) 389 IU/L; prothrombin time 46 second; activated partial thromboplastin time (APTT) 128 second international normalized ratio (INR) 5.2; fibrinogen 1.2 g/L; ammonia 69 micromol/L. There was no spontaneous bleeding. He received fresh frozen plasma (10 mL/kg). Echocardiography showed normal structure apart from a generous interatrial communication with predominant left to right shunt. There was a global pericardial effusion measuring 5 mm in four chamber view in diastole, with a larger pocket located anteromedially (►Fig. 1). There was a good biventricular function and no evidence of tamponade.

Over the next 6 hours, he developed progressively worsening hypotension (lowest invasive BP [blood pressure] of 31/18, mean: 23) refractory to volume boluses and multiple inotropes (Dopamine 20 microgram/kg/min; Dobutamine 20 microgram/kg/min; adrenaline 0.5 microgram/kg/min) in escalating doses. Blood pressure started to improve after commencing hydrocortisone (2 mg/kg/loading dose, once followed by 1 mg/kg/dose 6 hourly). Cortisol level was not obtained prior to commencing. In view of multitude of problems he was transferred to the Children's Hospital for further management.

Echocardiography on admission to the Children's Hospital confirmed the same findings.

Inotropes were weaned slowly and stopped after 48 hours. He was extubated to continuous positive airway pressure (CPAP) on day 3 and hydrocortisone was stopped the next

day. He remained normotensive without hydrocortisone until day 19. Pericardial effusion was also completely resolved over next 2 weeks. Haematological findings were investigated. Kleihauer's test result indicated 37 mL fetal blood loss that accounted for the initial anemia (Hb 83 g/L). However, white cell count was elevated ($30.1 \times 10^9/L$) and blood film showed blast cells ($2.1 \times 10^9/L$). Although the initial platelet count was normal ($190 \times 10^9/L$) there was a subsequent drop in the count over next few days (lowest $26 \times 10^9/L$). This prompted a bone marrow examination that showed 15% blast cells confirming the diagnosis of TMD. The thyroid function test revealed a raised TSH (thyroid stimulating hormone; 28.05 mIU/L) and low normal T4 (14.6 pmol/L) confirming subclinical hypothyroidism. He was commenced on L-thyroxine treatment that normalized thyroid function.

On day 19, he developed an acute deterioration with severe hypotension (lowest BP 39/12 with the mean of 21 mm Hg), was mechanically ventilated and commenced on volume bolus followed by inotropes (Adrenaline 0.2 microgram/kg/min and Dobutamine 10 microgram/kg/min) to which he did not respond. He was then restarted on hydrocortisone at 1 mg/kg/dose 6 hourly with good response. Unfortunately, no cortisol level was obtained prior to commencing on hydrocortisone. He was continued on maintenance dose of hydrocortisone with a view to wean it at a later stage and perform an ACTH (adrenocorticotropic hormone) stimulation test (synacthen test); however, this was not achieved prior to his death.

He developed progressive liver failure, splenomegaly with ascites. Investigations showed elevated transaminases and deranged coagulation profile. TORCH screening (Toxoplasma, Others, Rubella Cytomegalovirus, Herpes Simplex Virus), metabolic work-up including $\alpha 1$ antitrypsin, urine metabolic screen, and transferrin isoform were negative. Tense ascites needed peritoneal drainage of large amount of transudate. Ultrasound showed coarse echogenicity consistent with liver fibrosis/cirrhosis and collaterals suggestive of portal hypertension.



Fig. 1 Echocardiographic image showing pericardial effusion.

Multidisciplinary team opined that in view of continued deterioration despite maximal supportive therapy in the background of multiple issues, redirection of care was thought to be in his best interest. The family accepted the offer of palliative care course. He died on day 39, soon after extubation in the presence of his family. The post mortem autopsy was not performed as per the parental request.

Discussion

Our case with DS exhibited isolated PE without hydrops, TMD, hypothyroidism, liver failure with portal hypertension and possible adrenal insufficiency. The literature review (summarized in ►Table 1) was undertaken to establish the etiopathogenesis, presentation, associated findings, natural course, and management of fetal and neonatal pericardial effusion.

Pathogenesis of PE in DS

Mechanisms producing isolated PE in fetus/neonate are not completely understood. TMD develops in 3 to 10% of newborns with DS,⁵ is characterized by clonal proliferation of blast cells in blood/bone marrow and may be responsible for pericardial effusion.^{1,2,4,6–13} Pericardial effusion in TMD may occur due to myocardial infiltration by degranulating eosinophils¹³ or epicardial infiltration by atypical myeloid cells.¹⁰ It is also presumed that effusion could be related to an abnormal production of cytokines at the effusion site.⁶ PE has been demonstrated to be in association with hypothyroidism and celiac disease in early childhood^{3,14–16} but not in the perinatal period. Our case had both TMD and hypothyroidism.

Age of Onset

Most of the reported cases have been diagnosed either in the second or third trimester as PE is easily detected with ultrasound. PE has been diagnosed as early as (11^{6/7}–16^{4/7}) weeks.² Sharland and Lockhart¹⁷ reported 35 cases of PE detected at 18 to 25 weeks gestational age (GA) out of which 9 were confirmed to have DS arguing the importance of fetal karyotyping in cases of PE. Our case was diagnosed at 20 weeks GA and was monitored in utero. The others^{1,6,8–10,12,13} have diagnosed them at 30 to 36 weeks GA. Two cases were diagnosed in neonatal period (2 weeks) as one of them had no antenatal care⁴ and the authors have not reported about antenatal screening in other case.⁷ Al-Kasim et al¹¹ have reported six cases of PE, all diagnosed within 2 weeks of birth at full term gestation except one who was diagnosed at 35 weeks.

Cardiac Manifestation

In most reported cases the heart was structurally normal but some have reported associated ASD (atrial septal defect),^{4,11} VSD (ventricular septal defect),^{1,11} dextrocardia,¹⁷ and PDA (patent ductus arteriosus).¹¹ PE has been reported to be either isolated or associated with hydrops,^{2,8,10,11} manifesting either without cardiovascular compromise^{1,4,6,13,17} or with cardiac tamponade^{7,9–11} needing intervention. Isolated PE has been reported to progress to worsening hydrops^{2,8,10,11} and intra uterine death² or complete resolution.¹¹ Our case presented with isolated PE with no structural

cardiac anomalies or cardiac tamponade and resolved spontaneously.

Associated Malformation

Hepatomegaly,^{2,4,6–8,10,11,13} splenomegaly,^{2,8,10,11,13} skin nodules,¹¹ and petechiae¹² raises the possibility of TMD and has been consistently found in most of the cases of PE.^{1,2,4,6–8,10–13} Occasionally, PE can be associated with acute myeloid leukemia⁹ and congenital hypothyroidism.¹ Our patient had TMD and hypothyroidism. An interesting finding in our case was the temporal association between the administration of hydrocortisone and resolution of circulatory collapse on more than one occasion creating a convincing argument for possible adrenal insufficiency. Such an association has not been previously reported to the best of our knowledge.

Treatment

In utero

Pericardiocentesis in utero^{8–10} has been occasionally attempted successfully so as to prolong the pregnancy but others have chosen expectant management^{1,6,12,17} when PE was not associated with cardiovascular compromise.

Postnatal

Isolated PE can be managed expectantly until its spontaneous resolution. Sharland and Lockhart¹⁷ have reported complete resolution of PE without treatment in one preterm (28 weeks) and two term neonates. Pericardiocentesis is usually undertaken when PE leads to either cardiac tamponade⁷ or contributes to significant respiratory compromise.^{4,6,13} A short course of steroid (prednisolone) therapy for 2 weeks^{1,4,7} has been used to facilitate resolution of PE. Occasionally a prolonged course of steroid over 6⁶ to 12 weeks¹³ was required to achieve resolution of PE. Most of the cases of PE are associated with TMD. TMD has favorable outcome with complete remission within the first 3 months in most cases; however, in infants with severe and life-threatening symptoms (high white cell count, bleeding diatheses, liver fibrosis, and effusion) treatment with low dose cytarabine (1 mg/kg/day × 7 days) has a beneficial effect.¹⁸ In two term neonates with haemodynamically significant PE associated with TMD, a short course of cytarabine resulted in remarkable improvement and resolution of PE.¹¹ Oh et al¹² have used low-dose cytarabine in their patient with a large PE associated with TMD to prevent the development of hepatic fibrosis and achieved complete resolution of PE and TMD. In one of the case reports¹ thyroxine was used for hypothyroidism but it was started when PE had already resolved with steroid therapy. In our case, the short course of hydrocortisone for first 3 days given for the management of hypotension may have expedited resolution of PE. It had already resolved by the time thyroxine was commenced, thereby negating its role in facilitating PE resolution in our case.

Outcome

The outcome of neonates with PE in DS is difficult to ascertain as sometimes the parents opt for termination of pregnancy.^{10,17} The prognosis is worse if PE is associated

Table 1 Review of literature of pericardial effusion in Down's syndrome

Reference	No of patients	GA /weight at birth	Age of onset/ detection	Presenting features	Size of PE	Associated structural and functional defects of heart	Associated anomalies	Treatment	Outcome
Hirashima 2000 ¹	1	35 wk, 2,044 g	Antenatal: 34 wk	Isolated PE	Not reported	VSD(7 mm); no cardiovascular compromise	TMD and hypothyroidism	Steroid on d 8 (prednisolone 2 mg/kg/d), thyroxine on day 100, VSD closure at 81 d	PE began to decrease after steroid therapy on d 8 and resolved completely
Smrcek 2001 ²	11	Not reported	Antenatal: 5 cases at 11 ^{6/7} –16 ^{4/7} wk; 6 cases: at 18 ^{1/7} –32 ^{5/7} wk	In utero hydrops (4 babies also had hepato-splenomegaly)	Not reported	Normal structure; hydrops	TMD in 4 cases	No in utero intervention	4 cases: in utero fetal death (GA 28 ^{0/7} , 29 ^{6/7} , 30 ^{3/7} , 31 ^{5/7}); 7 cases: outcome not reported
Shenoy 2008 ⁴	1	Full term, 3,390 g.	Postnatal: 2 wk	Respiratory distress, hepatomegaly	Moderate	ASD (3 mm); no cardiovascular compromise	TMD	Pericardiocentesis (40 mL); steroid (prednisolone 2 mg/kg/d) for 10 d	PE resolved in 10 d; TMD resolved in 3 mo
Shitara 2017 ⁶	1	37 wk, 2,413 g	Antenatal: 36 wk	Hepatomegaly, respiratory compromise on d 5	Not reported	Normal structure; no compromise	TMD, eosinophilia, GATA1 mutation	Pericardial fenestration with chest drain; prednisolone 2 mg/kg/d from the 10th–51th d of life	Resolution of PE and TMD, discharge home on 49th d
Buyukkale 2012 ⁷	1	40 wk weight: not reported	Postnatal: 13 d	Respiratory distress, hepatomegaly	Not reported	Cardiac tamponade	TMD	Pericardiocentesis followed by a pericardial drainage tube; steroid (prednisolone) therapy after reaccumulation due to removal of drainage tube, steroid \times 1 wk	Complete regression of PE following steroid therapy; at 4 mo of age cardiac echocardiogram was normal and TMD had resolved
Strobelt 1995 ⁸	1	35 wk, 2,120 g	Antenatal: 31 wk	Hepato-splenomegaly noted at 31 wk and progressing to hydrops at 33 wk	Not reported	Normal structure and function	TMD diagnosed by cordocentesis at 31 wk	In utero: pericardiocentesis 40 mL at 33/40, no reaccumulation, no hydrops; ex utero: PE with normal heart on echocardiography but no treatment required	Spontaneous resolution of PE and TMD at 1 mo
Azancot 2003 ⁹	1	32 ^{2/7} wk, weight not reported	Antenatal: 31 wk	Isolated PE	12 mm	Normal structure; abnormal diastolic function	AML	In utero: pericardiocentesis	Termination of pregnancy at 32 ^{2/7} wk
Rougemont 2010 ¹⁰	1	32 wk; weight: not reported	Antenatal: 30 ^{3/7} wk	Hydrops	8 mm	Normal structure and function	Myeloid proliferation	PM findings: PE of 36 cc, hydropic with hepatosplenomegaly	Termination of pregnancy at 32 wk
Al-Kasim 2002 ¹¹	6	5 babies: full term; 1 baby: 35 wk; weight: not reported	Postnatal: 35 wk at birth, full term: 3 at birth, 1 at 7 d and 1 at 14 d	5 term infants presented with hepatosplenomegaly, 2 of them had respiratory distress and skin nodules; preterm (35 wk) hydrops with splenomegaly	Not reported	1 term neonate: tamponade; 35 wk preterm hydrops; 2 term neonates: ASD, VSD, PDA; 1 term neonate: ASD, PDA	TMD in all 6 cases	1 term neonate: pericardiocentesis and pericardial drain, 2 term neonates: Ara-C for 7 d; 4 neonates no treatment needed in	Spontaneous resolution of PE in 4 babies; resolution following Ara-C therapy in the other 2 babies; one of these babies developed AMKL at d 185 and died at d 204.

Table 1 (Continued)

Reference	No of patients	GA /weight at birth	Age of onset/ detection	Presenting features	Size of PE	Associated structural and functional defects of heart	Associated anomalies	Treatment	Outcome
Oh 2014 ¹²	1	35 wk, 2,700 g	Antenatal: 32 wk	Petechiae	22 × 13.6 × 12 mm	Normal structure and function	TMD	short course of low-dose cytarabine for TMD	Resolution of PE and TMD by 4 mo, AMKL at 4 y, cancer free at 5 y
Kusanagi 1998 ¹³	1	35 wk, 2,478 g	Antenatal: 35 wk	Hepatosplenomegaly.	Not reported	Thickened inter ventricular septum/normal function	TMD and hyper eosinophilic syndrome	Pericardiocentesis: 14 mL showed eosinophils; steroid (prednisolone 2–5 mg/kg/d) for 12 wk	Pericardial effusion, cardiomegaly and TMD resolved after 8 wk.
Sharland 1995 ¹⁷	9	1 baby: 28 wk; 2 other babies: full term. remaining 6–terminated in utero; weight not reported	Antenatal: 18–25 wk	Isolated PE	2–4.5 mm	1 baby had dextrocardia with normal structure; all had normal function		6 pregnancies terminated in utero; other 3 required no treatment	Spontaneous resolution of PE in all 3 babies

Abbreviations: AMKL, acute myelokaryoblastic leukaemia; AML, acute myeloid leukemia; Ara-C, cytosine arabinoside; ASD, atrial septal defect; GA, gestational age; PDA, patent ductus arteriosus; PE, pericardial effusion; PM, post mortem; TMD, transient myeloproliferative disorder; VSD, ventricular septal defect.

with hydrops fetalis as the risk of intrauterine death is very high as reported by Smrcek et al² in 4/11 cases with hydrops. Occasionally, a spontaneous resolution¹¹ or reversal of hydrops by in utero pericardiocentesis and complete resolution of PE has been achieved.⁸ PE associated with TMD^{1,4,6–8,11–13} had complete resolution of PE either spontaneously or with treatment. Our index case had liver fibrosis associated with TMD. The outcome is fatal when liver fibrosis develops with TMD. The literature review shows that 94% of DS cases with TMD complicated by liver fibrosis had died by the age of 150 days.¹⁹ Our case had similar outcome, although we had chosen the palliation pathway in agreement with family due to liver failure.

Conclusion

Our case report along with a comprehensive review of other case reports of perinatal onset of PE in DS indicate that PE can be isolated or part of hydrops, asymptomatic or present with tamponade, can have associated cardiac and noncardiac anomalies, the most common being TMD. PE in association with TMD and liver failure has been reported to have a poor prognosis as in our case. PE usually resolves spontaneously but sometimes need medications (prednisolone/cytarabine). PE associated with adrenal insufficiency in DS has not been previously described. While not proven, we assume this baby had adrenal insufficiency based on the temporal association between resolution of hypotension and commencement of hydrocortisone at two different time points during the course.

Ethical Approval

The article is a case report and does not contain any studies with human or animal participants performed by any of the authors. The scientific report does not reveal patient identity anywhere.

Conflict of Interest

The authors declare that they have no conflict of interest.

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