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CASE REPORT

Cough as a symptom of respiratory infection or a rare cardiological pathology in an infant

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ABSTRACT

Congenital coronary artery anomalies are rare and represent 0.24–0.46% of all congenital heart defects. The most common is an anomaly in which the left coronary artery arises from the pulmonary artery (ALCAPA), also known as a Bland-White-Garland syndrome. Nonspecific symptoms typically appear at 2–3 months of age. We present the case of a 10-week-old boy admitted to the hospital due to cough and dyspnea, with suspicion of a respiratory tract infection with no clinical improvement after standard therapy. The chest X-ray revealed cardiomegaly. The electrocardiogram showed signs of anterolateral infarction. Echocardiography revealed signs of dilatated cardiomyopathy and color Doppler was of great value in establishing a final diagnosis. After confirming the diagnosis of ALCAPA in computed tomography angiography, the patient was operated on, with a good outcome.

KEY WORDS:

cough, dyspnea, cardiomegaly, coronary artery.

INTRODUCTION

In the pediatric population respiratory infections are the most common reason for seeking a pediatric consultation. In most cases, they appear to be benign infections and resolve after symptomatic treatment. In the case of therapy failure or when life threatening symptoms (e.g. severe dyspnea, cyanosis, dehydration) are present, patients should be referred to a hospital. When the patient's condition does not improve with the standard treatment for infection, a heart pathology should be considered as the possible cause of cough, especially in cases with high level of N-terminal pro-brain natriuretic peptide (NT-proBNP).

CASE REPORT

A 10-week-old infant with body weight 5300 g, previously considered healthy (born at 40 weeks of gestation, Apgar score of 10 points, body weight 3220 g), was admitted to a general pediatric hospital because of dyspnea. According to the parents, the child presented symptoms such as cough and dyspnea for several days, with no fever. Also difficulties with feeding, sweating, anxiety and frequent crying were reported by the parents.

Upon admission to the pediatric department his general condition was considered to be quite good with dyspnea being the leading sign and suspicion of respiratory tract infection (pneumonia) was established.

Laboratory tests revealed the following: negative inflammatory markers (WBC 8.7×10^3/ul with normal peripheral blood smear, C-reactive protein within normal range), respiratory acidosis in capillary blood gasses (pH – 7.231, pCO_2 – 41mm Hg, pO_2 – 50 mm Hg) and a negative test for respiratory syncytial virus (RSV). Antibiotic (cefuroxime), nebulized ipratropium bromide and intravenous steroids were administered, but despite treatment the patient's condition worsened: saturation

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dropped to 70% and respiratory acidosis became more severe (pH –7.098, pCO_2 – 58 mm Hg, pO_2 – 47 mm Hg). The chest X-ray performed on the first day of admission revealed cardiomegaly and bilateral parenchymal atelectasis changes with hyperinflation. Due to cardiomegaly and worsening of the clinical condition, a cardiological consultation was requested. Echocardiography (ECHO) revealed significant left ventricle dilation and severely diminished left ventricular (LV) systolic function, which are typical for dilated cardiomyopathy (DCM). The patient was transferred to the cardiology department.

At the time of admission to the cardiology department the patient was in a poor general condition with signs of heart failure (HF) on physical examination: prolonged capillary refill time, tachycardia with a heart rate of 170 bpm, galop rhythm and a blood pressure of 55/35 mm Hg. Heart sounds were silent and a systolic murmur grade 2 on the Levine scale was best heard at the apex.

Oxygen saturation was 90–92% on room air. Capillary blood gases revealed a pH value of 7.364, pCO_2 – 46 mm Hg, pO2 – 54 mm Hg. He presented tachypnea and dyspnea (respiratory rate 70/min, intercostal retraction). Lung auscultation revealed bilateral crackles. The liver was enlarged, palpable 3 cm below the costal margin.

The chest X-ray (Figure 1) revealed an increased cardiothoracic index (0.72) and haziness in the upper right and upper and middle left lobes, as well atelectasis in the lower right lobe and slight right sided pneumothorax.

Twelve-lead electrocardiogram (ECG) (Figure 2) showed evidence of an infarction with the presence of deep Q-waves in leads representative for the left ventricle and raised the suspicion of coronary artery problem.

Echocardiography showed LV enlargement (37 mm; Z-score + 4.95) (Figure 3), moderate mitral regurgitation and severely diminished LV systolic function with extremely low ejection fraction (EF) measured using the Simpson method – 10% (norm ≥ 55%). The origin of the coronary arteries was not evaluated in the first ECHO because of the child's anxiety and lack of cooperation.

Blood tests showed very high levels of NT-proBNP (> 25 000 pg/l, norm < 125 pg/ml) and troponin I (3100 ng/l, norm < 19 ng/l). Pharmacological treatment for HF was initiated with intravenous diuretics and a phosphodiesterase inhibitor. High-flow nasal cannula therapy initiated for respiratory support.

Echocardiography was repeated and the origin of the left main coronary artery (LMCA) was not clearly visualized in the left Valsalva sinus, and retrograde blood flow through the pulmonary trunk during diastole as well as systolic and diastolic flow through the collateral circulation within the ventricular septum was present.

Additionally, mild dilatation of the right coronary artery (RCA) was visualized. Based on these findings, anomalous origin of the LMCA from the pulmonary artery (ALCAPA) was suspected. This diagnosis was con-

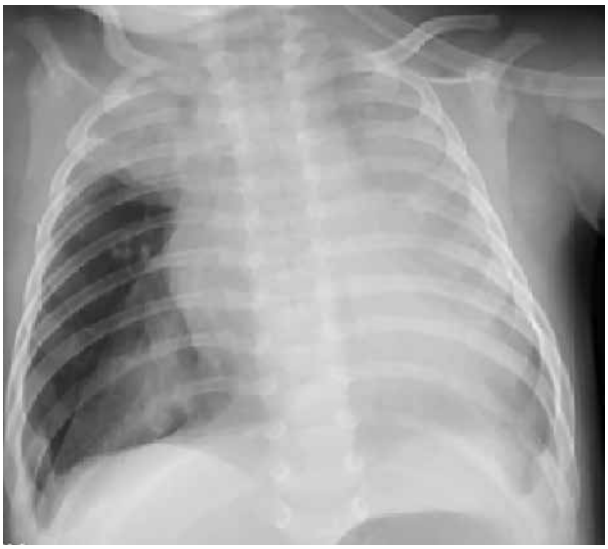

FIGURE 1. Chest X-ray demonstrating cardiomegaly with increased cardiothoracic index (CTI 0.72) and haziness in the upper right and upper and middle left lobes, as well atelectasis in the lower right lobe and slight right sided pneumothorax

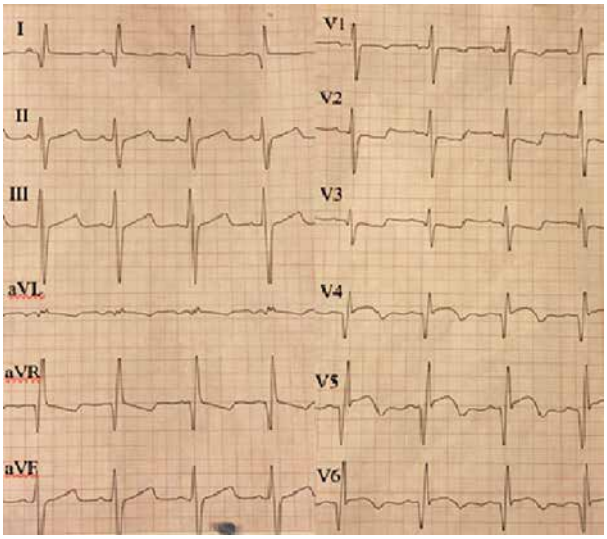

FIGURE 2. Standard electrocardiogram shows deep Q-waves in leads I and aVR and deep Q-waves with ST elevation in the left precordial leads (V4–V6)

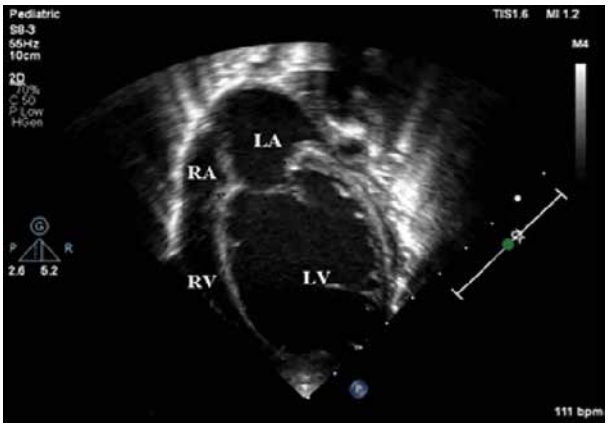

FIGURE 3. Echocardiography four-chamber view of the heart demonstrating enlarged left ventricle

firmed using computed tomography angiography (CT-angio).

The patient was qualified for urgent cardiac surgery with extracorporeal circulation as a life-saving procedure. The anomalous left coronary artery was reimplanted in the aorta. There were no significant complications in the postoperative period. A gradual improvement of the patient's condition, ECHO results and laboratory tests was observed. The left ventricle EF rose to 46% on the day of discharge from the hospital.

The concentrations of NT-proBNP and troponin I decreased significantly (NT-proBNP > 25 000–4000 pg/l; troponin I 3100–59 ng/l), but were still elevated.

The electrocardiogram showed changes indicating an evolution of LV myocardial infarction. The patient was discharged from the hospital 52 days after surgery with a recommendation to continue pharmacotherapy (carvedilol, captopril, spironolactone, digoxin, acetylsalicylic acid) for HF and regular check-ups.

DISCUSSION

Our 10-week-old boy was brought to the general pediatric hospital with suspicion of respiratory tract infection due to persistent cough. Non-infectious causes of cough in children include foreign body aspiration, asthma, allergy, gastroesophageal reflux disease and HF, and should always be taken into consideration in the diagnostic work-up.

Additional signs typical for lower respiratory tract infections include tachypnea, dyspnea, wheezes, and crepitations, which were almost all present in our patient.

Tachycardia can also accompany lower respiratory tract infections and fever.

Of note, those signs could also be present in any conditions leading to HF, such as congenital heart defects, especially coarctation of the aorta and aortic valve stenosis in the newborn period and/or infancy. Also in early infancy, non-cyanotic congenital heart defects with left to right shunts could be responsible for HF after pulmonary resistance decreases. Supraventricular tachycardia, being the most frequent symptomatic arrhythmia in children, as well myocarditis, could also lead to HF.

The parents of our patient also reported difficulties with feeding. It is one of the most commonly reported symptoms of HF in infants, occurring together with poor weight gain. In infants and small children the Ross scale is used to assess HF severity. One of the parameters included is the volume of milk consumed during a single feeding, as well as feeding time. This scale also includes the assessment of pattern and frequency of breathing, the heart rate, the presence of a third heart sound, enlargement of the liver and the assessment of peripheral perfusion.

In a child with left ventricle failure, apart from tachypnea and dyspnea, during lung auscultation we can hear crackling sounds and rales resulting from lung congestion. Of note, in small infants severe lung congestion could also compress the soft bronchi and bronchioles, and wheezing, typical mostly for obstructive bronchitis and asthma, could also be heard.

Other symptoms of HF include tachycardia, gallop rhythm, sweaty skin, cold extremities, prolonged capillary refill and weak peripheral pulse, hypotension, hepatomegaly and peripheral edema.

Tachycardia can accompany a fever and each 1°C can raise the heart rate by about 10–15 bpm. Fever was not present in our infant, which should raise suspicion for a cause other than respiratory infection for the infant's condition.

Typical symptoms for right ventricle failure, such as hepatomegaly, were also present in our patient.

During auscultation of our patient's heart, we noted a soft systolic murmur at the apex with an intensity of grade 2 on the Levine scale. The murmur appeared as a consequence of LV and mitral valve annulus dilatation, which subsequently caused mitral regurgitation.

Negative inflammatory markers did not support the infection theory of the presenting symptoms and signs in our infant. The evaluation for RSV infection was also negative.

Very high levels of troponin and NT-proBNP were noted in our patient. Troponin I is a marker of cardiac ischemia. NT-proBNP levels correlate with the severity of HF.

During the neonatal stage the norms of NT-proBNP and troponin levels are higher than in older children or adults. Moreover, what sometimes make diagnostics difficult, NT-proBNP (but generally not troponin) can be elevated not only in HF but also in severe respiratory tract infections in children with an anatomically healthy heart. However, the level of NT-proBNP is then lower than in HF cases. According to available studies reviewed by Edwards *et al.* [1], in a group of 1000 children with bronchiolitis the median NT-proBNP level was 241 pg/ml, whereas in children with cardiac failure it was above 7321 pg/ml. In our patient NT-proBNP was above 25 000 pg/ml, which strongly suggested a cardiological cause of the symptoms.

In the present case, heart enlargement with a cardio-thoracic index of 0.72 was described in the chest X-ray. The cardio-thoracic index is the quotient of the maximum size of the heart and the chest. Its normal value in newborns is about 0.6 (resulting from a more horizontal position of the heart in the chest) and it decreases with age to 0.5 due to a more vertical orientation of the heart [2]. An increased cardio-thoracic index value with signs of HF raised suspicion of a heart problem as a major cause in our patient.

The causes of cardiomegaly in children include, for example, congenital heart defects, myocarditis, pericarditis, cardiomyopathies, long episodes of arrhythmia, and severe arterial hypertension.

In a study by Zheng *et al.*[3] summarizing the experiences of patients with ALPACA, the most common findings in chest X-rays were cardiomegaly, pulmonary trunk dilatation, as well pulmonary edema in younger children.

The standard ECG in our patient showed ST elevation in leads V5 and V6, consistent with coronary ischemia, and pathologic Q-waves in leads I, aVR, V5, and V6 – typical for myocardial infarction. Typical ECG changes due to anterolateral myocardial infarction include abnormal Q-wave, ST segment changes and T-wave inversion [4–6]. According to data from the literature, about 20–45% of patients with ALCAPA do not show an abnormal Q-wave in ECG and the only change is abnormal progression of R-waves in chest leads [3].

Echocardiography is the basic examination used in the diagnosis of heart pathology. In our patient transthoracic ECHO showed severely impaired LV systolic function with extremely low EF (10%) and LV dilatation, consistent with the diagnosis of DCM. Dilated cardiomyopathy is characterized by LV dilatation and dysfunction, resulting in diminished cardiac output and secondary congestive HF. It is the most common cardiomyopathy, comprising 50–60% of children with cardiomyopathy. In our patient transthoracic ECHO raised the suspicion of coronary abnormality as a cause of DCM.

In an anatomically healthy child the right and left coronary arteries should arise from the right and left coronary sinus of Valsalva, respectively [7]. In ALCAPA, which is the most common variation of abnormal coronary origin in children, the LMCA arises from the pulmonary artery and in postnatal life is perfused with unoxygenated blood.

During fetal life this anomaly is well tolerated as blood in the pulmonary trunk is well saturated, and is at a high pressure [8]. After birth, blood in the pulmonary artery becomes desaturated and its pressure decreases, while the left ventricle's oxygen demand is steadily increasing.

This disproportion starts to be symptomatic at about 2–3 months of life when the myocardium becomes ischemic, initially causing nonspecific signs and symptoms that may be mistaken for a respiratory infection [9].

The identification of the origin of the left coronary artery in ECHO can be challenging; one can sometimes even falsely visualize the wrong origin of the LCA when its course is close to the proper ostium. In such situations aortography is used to confirm the diagnosis [10].

Visualization of abnormal diastolic flow in the pulmonary artery in ECHO and a dilated RCA with collateral circulation between the right and left coronary artery in the ventricular septum, with signs of DCM, can also be useful to establish diagnosis of ALCAPA [10, 11]. The diastolic flow in the pulmonary artery is caused by higher blood pressure in the right than in the left coronary artery and pulmonary trunk. The pressure gradient results in blood flow from the right to the left coronary artery collateral circulation and further to the pulmonary artery.

Currently, the gold standard for confirmation of ALCAPA is angio-CT [11]. According to a study by Roik *et al.* [12], in a group of 110 neonates and infants with congenital heart diseases, the orifices of the left coronary artery were visible in 100% of the performed angio-CT scans.

In the present case, the symptoms worsened at 3 months of age, masked by a respiratory presentation. The lack of improvement after standard therapy for infection and results of specific cardiac tests led to the final diagnosis. Disturbing symptoms reported by parents may also include excessive crying mistakenly associated with an intestinal colic pain. In a study describing 3 cases of ALCAPA by Ma *et al.* [13], the reason for hospitalization was symptoms of respiratory infections, as in our case. The course of ALCAPA is more severe in infants. As in the present case, the symptoms of HF resulting from impaired LV systolic function are the most common and require pharmacological treatment.

Our patient, prior to the operation, received an intravenous infusion of milrinone and furosemide. Usually, drugs that improve contractility of the heart muscle with the addition of loop diuretics are the first-line drugs in the treatment of acute HF.

In chronic conditions the pillars of HF management are angiotensin-converting enzyme inhibitors responsible for reducing afterload (e.g. captopril, enalapril), β-blockers (e.g. metoprolol, carvedilol) and aldosterone antagonists (e.g. spironolactone). Each of these agents works through a different arm of the sympathetic nervous system or renin-angiotensin-aldosterone axis.

β-blockers, by reducing the heart rate, also lower the heart's need for oxygen. Moreover, by prolonging the diastolic phase, they improve the blood supply to the heart muscle. Because of its effect on lowering blood pressure it is important to ensure that the child is properly hydrated.

Chronic HF management in children also includes thiazides and loop diuretics to achieve a euvolemic state.

Digoxin, which was previously used more widely, has now been advised to be used at low doses in symptomatic, rather than asymptomatic, LV dysfunction. The disadvantage of digoxin is a narrow spectrum between the therapeutic and toxic doses.

In the course of differential diagnosis of DCM, other causes of LV enlargement and/or impaired contractility should be considered, and examples are given in Table 1.

Diagnosis of ALCAPA is an indication for cardiosurgical treatment and should be done as soon as possible. It involves the excision and reimplantation of the anomalous coronary artery from the pulmonary artery into the aorta [14, 15]. The results of surgical repair are usually good, and the median normalization time of LV function is about 6 months. Postoperative complications may occur and mainly include coronary artery stenosis. In a study by Gao *et al.* [14] the early mortality rate was 7.7%

TABLE 1. Examples of pathology with cardiomegaly, increased N-terminal pro B-type natriuretic peptide and left ventricular failure

Parameters	Symptoms	Signs	Time of onset	Lab tests (troponins, NT-pro BNP)	ECG	Imaging tests
ALCAPA	– HF – excessive crying (due to chest pain resulting from myocardial ischemia)	– systolic murmur at the apex due to MR – LVF	– 2– 3 months of age – symptoms gradually increase	– ↑ troponin – ↑ NT-pro BNP	– ST-T segment elevation – deep Q-waves in LV leads	ECHO: – visualization of origin LMCA from MPA – a dilated RCA – an abnormal diastolic flow in MPA – ↑ LV ↓ SF ↓ EF – severe MR – hyperechogenic papillary muscles Angio-CT: – the gold standard to visualize coronary artery origin
DCM	– HF exercise intolerance	– systolic murmur at the apex due to MR – LVF	– could be preceded by infection and myocarditis – beginning at different ages – symptoms are progressive, less frequent suddenly	– ↑ NT-pro BNP – ↑ or ↔ troponin	– LAE – LVH – depolarization abnormalities – nonspecific intraventricular conduction delay or LBBB – pathological Q- waves – arrhythmias	ECHO: – ↑ LV – ↓ SF ↓ EF – MR CMR: – differential diagnosis between ischemic and non-ischemic DCM – ↑ ventricular volumes, – ↓ EF
TIC	HF	– HR ≥ upper limit for age – LVF	– onset in every age group after a longer duration of tachycardia	– ↑ or ↔ NT-pro BNP – ↑ or ↔ troponin	– SVT	ECHO: – ↑ LV – ↓ SF ↓ EF – usually without an anatomical heart defect
VSD	HF	– harsh systolic murmur max. at Erb's point with radiation to liver – LVF	– about 2–3 months of age with decrease in pulmonary resistance	– ↑ NT-pro BNP	– initially within the normal range, then features of LVH	ECHO: – VSD visualization – L – > R shunt – ↑ LV, ↑ LA – dilatated MPA – ↑ Qp:QS ratio (> 1.5– 2 : 1) in hemodynamically significant defect
MC	– chest pain – HF	– LVF – infection (few days/ weeks earlier)	– onset in every age group – in fulminating cases symptoms appear suddenly	– ↑ troponin – ↑ inflammatory markers – ↑ NT-proBNP – positive viral tests (e.g. parvovirus B19, adenovirus, coxsackie, flu)	– tachycardia – depolarization abnormalities in every lead – low QRS voltage – arrhythmias	ECHO: – ↑ LV – ↓ SF ↓ EF – MR CMR: – inflammation of the cardiac wall – ↓ EF – MR – LGE

ALCAPA – anomalous left coronary artery from the pulmonary artery, CMR – cardiac magnetic resonance, DCM – dilatated cardiomyopathy, ECHO – echocardiography, EF – ejection fraction, HF – heart failure symptoms (cough, dyspnea, feeding difficulties, low weight gain, sweating), HR – heart rate, LA – left atrium, LAE – left atrial enlargement, LBBB – left bundle branch block, LGE – late gadolinium enhancement , LMCA – left main coronary artery, LV – left ventricle, LVF – left ventricular failure signs (tachycardia, tachypnea, crackles), LVH – left ventricle hypertrophy, MC – myocarditis, MPA – main pulmonary artery, MR – mitral regurgitation, NT-proBNP – N-terminal pro B-type natriuretic peptide, Qp – pulmonary blood flow, Qs – systemic blood flow, RCA – right coronary artery, SF – shortening fraction, SVT – supraventricular tachycardia, TIC – tachycardia induced cardiomyopathy, VSD – ventricular sepal defect, ↑ – increase/dilation, ↓ – decrease, ↔ – at normal range, L→R shunt – shunt from left to right ventricle

and the late mortality rate was 3.8%, resulting from end-stage HF and arrhythmia. Patients after treatment require lifelong cardiological follow-up [16].

CONCLUSIONS

Although ALCAPA is a very rare congenital anomaly, it should be taken into consideration as a differential diagnosis in children with symptoms such as cough and dyspnea, mainly typical for respiratory infection, but also for LV failure. Immediate selection for cardiac surgery significantly improves the prognosis.

DISCLOSURE

The authors declare no conflict of interest.

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