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CASE DESCRIPTION

Is negative neonatal screening for cystic fibrosis sufficient to rule out the diagnosis?

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Introduction

Cystic fibrosis (CF) is a genetic multi organ disease occurring mainly among Caucasian children [1, 2]. Clinical picture of cystic fibrosis varies. Classical form is typical for the presence of pulmonary symptoms caused by pancreatic insufficiency [2]. In infant age, the first sign of CF can take form of a severe disorder of acid-base balance and electrolytes. The latest statistical data published by Slovak authors from a neonatal screening centre indicate that incidence of the disease in Slovakia in the past five years reached 1:7668 liveborn children [3, 4]. Phenotype of disease correlates with presence of two mutations in a CFTR gene – cystic fibrosis transmembrane conductance regulator [5]. As a result of neonatal screening, mean age at the time of CF diagnosis went down to 6-8 weeks of age [6].

The article contains our observations in a 10-months-old child with negative neonatal screening test. It also stresses the importance of diagnostics based on clinical symptoms.

Patient description

The child was born from 4th physiological pregnancy. Perinatal history was physiological, too. The father had bronchial asthma, the 6-year-old sister was treated for pollinosis and cough at the Department of Immunology and Allergy and the 19-year-old foster brother (a common mother) also suffered from allergy. Results of neonatal biochemical screening for congenital hypothyroidism, phenylketonuria, congenital adrenal hyperplasia, inherited metabolic disorders and cystic fibrosis came out all negative.

At the age of three months, fibres of fresh blood occurred in the stool. At the age of 6 months, the child went down with upper respiratory tract viral disease with febrility up to 40°C, for which the infant was treated symptomatically. At the age of 8 months, a sudden face swelling occurred accompanied by breathing difficulties and body urticaria. The condition occurred right after the child had swallowed several spoons of curd cheese dessert. In response, parents administered few drops of Fenistil (dimetindene) to the child. Since the condition did not worsen, instead it faded away after 4 hours, the parents failed to call upon a doctor.

The child was first hospitalised at the age of 10 months, in hot summer period, for failure to thrive and vomiting. Laboratory parameters upon admission indicated disorder of internal environment in terms of metabolic alkalosis.

Hyponatraemia reached 121 mmol/l, hypokalaemia was 3.2 mmol/l and even more significant was the hypochloraemia – 76 mmol/l. Immunological profile examination confirmed increased IgE and positive specific IgE for wheat flower, egg and cow's milk (see Table 1). Renal functional tests proved no renal ion loss.

Table 1. Laboratory parameters at patient's age of 10 months.

Laboratory parameters	Lab results
Na	121 mmol/l
K	3,2 mmol/l
Cl	76 mmol/l
Specific IgE	> 2000 IU/l
Specific IgE (wheat)	3,1 IU/ml
Specific IgE (eggs)	5,36 IU/ml
Specific IgE (cow's milk)	9,06 IU/ml
Chlorides in sweat	56 mmol/l

The child was transferred to the Department of Pediatric Pneumology and Phtiseology in Podunajské Biskupice for further testing due to border findings of the sweat test performed on patient's back (chlorides in sweat: 56 mmol/l) with a diagnosis of malabsorption and allergy to cow's milk protein, wheat and eggs.

During hospitalisation, we repeated the test on the child's forearm and the result in both samples satisfied the reference span. Results of further laboratory testing showed no pathology. Despite negative neonatal screening for cystic fibrosis and negative chloride sweat test results, we sent a blood sample for genetic examination.

Molecular genetic testing showed presence of two CFTR gene mutations.

The patient is a compound heterozygote for delF508/3849+10kbCT mutation and such mutation ranks among 1 to 2% of mutations which may result in negative chloride sweat testing [5, 6].

The child remained hospitalised in our centre to be monitored for cystic fibrosis.

Discussion

Screening of cystic fibrosis was launched in Slovakia on September 1, 2009. It is based on measurement of the immunoluminometric trypsinogen (IRT) in a dry blood drop via neo IRT ILMA KIT [7]. Global data concerning false negative CF results are from 5 to 9% [8, 9], while in Slovakia we have duly registered seven cases.

In case of false negative result of screening, the child loses the chance for early diagnostics. Those are the cases when diagnosis comes late based on clinical symptoms of disrupted internal environment during acute febrile

illness, accompanied by vomiting and diarrhoea. As a result of steep chloride losses via sweat and stool, salts are depleted and hypochloraemic alkalosis occurs. The disorder becomes even more profound in case of insufficient compensation and nutrition lacking salt (breastfed or formula milk) [6, 10].

However, metabolic alkalosis may also be found in children with CF without acute febrile illness as a result of prolonged profound salt loss via sweat. Clinical symptoms include: loss of appetite, failure to thrive, agitation and vomiting. A child may not be significantly dehydrated and due to chronic lack of salt, pseudo-Bartter's syndrome [10, 11] may occur during intercurrent infection. Recent study by Swedish authors documents 17 cases of children with originally negative neonatal cystic fibrosis testing. The first disease manifestations were registered as a result of pseudo-Bartter's syndrome signs [9, 12].

Differential diagnostics relies to a great extent on sodium concentration and urine chloride test levels. In our case, no urine electrolyte losses were found, which would be accompanied by hypoelectrolytaemia, as a typical manifestation of Bartter's syndrome with genetic defect of tubular function in the segment of ascending limb of loop of Henle.

Another interesting feature of this case is the fact that chloride sweat test results differed in two different locations. A large number of sweat glands is located on forearm flexors. For this reason, sweat test is usually performed on a forearm. Other locations, including the back, may cause the results to be doubtful. Back is a large area and sole placement of electrodes may in some cases cause allergic response. Since CF diagnosis is a very serious piece of information for a parent, confusing result may cause avoidable worries. It is ideal for a sweat test to be performed by experienced laboratory staff dealing with at least 250 examinations annually.

Molecular genetic examination proved that the child described here is a compound hetero-zygote for CFTR gene mutation – apart from „classical" mutation (delF508), the child is also a bearer of 3849+10kbCT mutation which, from a functional viewpoint, belongs to the 5th class of CFTR gene mutation. Such cases are characterised by reduced production, impaired transport and lowered amount of fully functional CFTR protein on apical membrane. This mutation is one of 65 CFTR gene mutation which are currently being tested in Slovakia when cystic fibrosis is suspected. See the most common CF mutations in Slovakia in Table 2. Mild course of disease is typical for this disease, which occurs in its atypical and monosymptomatic form. It is ranked among 1 to 2% of mutations which may result in negative chloride sweat test results [5, 11].

The child in our case study showed profound allergic response and subsequently, allergy to several foodstuffs was confirmed. Incidence of food allergies in children with cystic fibrosis was investigated in a retrospective study from 2009 to 2013 by Bogota authors. Among 30 patients in a sample group, food allergy was confirmed in 14.8 % [13].

Conclusions

To conclude, we would like to point out the fact that neither negative result of biochemical screening nor normal finding from chloride sweat test may completely rule out the diagnosis of cystic fibrosis and in the presence of clinical symptoms stirring suspicion for cystic fibrosis, further tests need to be run.

Table 2. The most common cystic fibrosis mutations in Slovakia.

Mutation	Origin (ethnicity)	Mutation	Origin (ethnicity)
1717-1G→A	France/Italy	2183AA→G	Tirols
G542X	Mediterranean	3569delC	Sweden
W1282X	Ashkenazi	1078delT	Breton
N1303K	Mediterranean	I507del	Anglo-Saxons
F508DEL	Europe	R347P	Central Europe
3849+10kb	Ashkenazi	R553X	Central Europe
CFTR2,3del	Slavs	3120+1G→A	Africa/Arab
394delTT	Baltic	2789+5G→A	Eastern Europe
G551D	Celts	R1162X	Northern Italy
R117H	Anglo-Saxons	R334W	Eastern Europe
A455E	Netherlands		

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Conflict of interest: none declared

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