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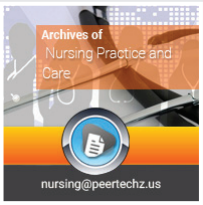

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Case Report

Can newborn screening be cost benefit procedure if preventing serious complications of cystic fibrosis?

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Abstract

Cystic Fibrosis (CF) is a common inherited disease with reported mean prevalence of 0.737/10,000 in 27 EU countries (Farrell J Cyst Fibros. 2008). Still, many EU countries have not implemented CF in the Newborn Screening (NBS) programme, including our country. We report the case of a 7-month-old boy whose presenting signs of CF were life-threatening neurological symptoms caused by severe metabolic alkalosis and hypoelectrolytemia. By presenting this case, we argue hoping to persuade the authorities in any country that the available newborn screening for CF is the cost benefit procedure in preventing life treating consequences with the obvious impact on the long-term prognosis of this chronic disease.

Introduction

Cystic fibrosis is an inherited disease, common among Caucasians, characterized by respiratory and/or gastrointestinal symptoms. Most common presentations include respiratory symptoms (40%), failure to thrive (29%), steatorrhea (24%), and meconium ileus (19%). Occasionally reported presentations include hypoelectrolytemia with dehydration, hematological abnormalities, and intracerebral hemorrhage, all known as life treating complications of CF and common in patients without prenatal/neonatal screening [1]. It is well known that the time of diagnosis correlates with an increased incidence of complications and the overall prognosis of CF. In patients with delayed diagnosis, reported mortality due to complications is about 5% of patients with CF [2]. The early diagnosis of CF based on neonatal screening is feasible by 2 months of age. Identifying potential patients with CF, besides the opportunity to prevent malnutrition and chronic *Pseudomonas aeruginosa* infections, enables clinicians to recognize potential serious complications. Informing the parents about symptoms of CF is of great importance in comparison with delayed diagnosis, the consequences, and the possible greater mortality risks of CF.

By reporting a case of a 7-month-old boy who presented with serious life treating neurological symptoms caused by metabolic alkalosis and hypoelectrolythemia, we intend not only to argue for implementing CF in the newborn screening program but to improve recognition and early diagnosis of CF, this chronic and not uncommon disease in our country.

Case report

A 7- month-old boy presented to the emergency department with one day history of unusual behaviour suggesting unspecific

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neurological symptoms and the 10-day history of poor appetite with occasional vomiting but without diarrea. On the morning, preceding the admission, he suddenly became lethargic, hardly responding to any stimuli, with an expressionless face, at periods staring for a few minutes and motionless. His previous medical history including pregnancy, delivery, birth weight, and early development was unremarkable, breastfed for a month, afterward with milk formula, and gained weight on 25 percentile. At the age of 6 months, he had his first respiratory infection, treated by antibiotics. The family history of young unrelated parents was negative for hereditary disease.

At admission, he was lethargic, at periods starring and motionless, hypotonic, but extremely pale with no rash. Except for mild dehydration, he had normal pupil reactions, showed no resistance to neck flexion, and the auscultation of lungs and hurt including abdominal palpation were unremarkable. Respiratory rate was 44/min, hurt rate 176/min, blood pressure 101/49 mmHg, capillary refill time <2 sec, temperature 36.3ºC, and body weight 6.8 kg (<5 percentile for age).

Initial biochemical tests showed severe hypoelectrolytemia (serum sodium 126 mmol/l, chloride 65 mmol/L, potassium 2,15 mmol/l, ionized calcium 1.05 mmol/L) and severe metabolic alkalosis (pH 7,67, bicarbonate 46.7 mmol/l, total CO2 47.9 mmol/l), mild anemia (Hb 96 g/dl), normal serum glucose, creatinine, proteins, liver enzymes and normal ammonium (32 umol/L). Possible intoxication and infection were excluded (C-reactive protein of 2.5 mg/L), including normal lumbal punction, normal chest radiography and abdominal ultrasound. Undertaken neurological evaluation revealed unremarkable ophthalmologist's exam followed by Electroencephalogram (EEG) showing abnormal high voltage delta activity of 2-3 c/sec, marked above temporal and occipital regions, with appearing of theta activity, suggesting brain edema. Computer Tomography (CT) of the brain excluded intracerebral hemorrhage, tumor, and possible trauma. Promptly initiated treatment with parenteral rehydration and antioedematous therapy resulted in correction of hypoelectrolythemia and metabolic alkalosis within 72 hours followed by gradual clinical and neurological recovery. Searching for the differential diagnosis of severe hypoeletrolytemic alkalosis (low potassium and chloride) due to low urinary excretion of electrolytes (Na 9, 9 mmol/l, K 9.9 mmol/L, Cl 10, 1 mmol/L) and low Plasma Rennin Activity (PRA 1,5 ng/ml/h) at admission, Bartter syndrome was excluded. Eventually, despite negative family history for CF, unusual sweating noticed from the second day following admission, prompted the diagnosis of CF definitively confirmed by chloride sweat test (113.6 and 98.8 mmol/L), law fecal pancreatic elastase test (< 15 ng/g), and genetic analysis showing homozygous ΔF508/ΔF508; 9T/9T genotype. He was discharged from the hospital in good health, without obvious neurological sequelae and normal control EEG analysis, starting adequate nutrition and supplementation with vitamins.

Followed up for 3 years, he had another 4 episodes of dehydration with mild electrolyte disbalance and metabolic alkalosis but without complications, all in the summer months. The parents were well informed about the nature of CF and the characteristic symptoms, so they could come to the hospital soon after he started vomiting.

Discussion

There are different presenting symptoms of CF [1]. Some authors classify them into five categories: respiratory symptoms, gastrointestinal symptoms, both respiratory and gastrointestinal symptoms, other less common symptoms (electrolyte imbalance, nasal polyps, rectal prolapse, and liver problems) usually in combination with respiratory and/or gastrointestinal symptoms and the fifth category, named after other presenting symptoms [3]. The presenting symptoms of CF can be different and life-threatening as in our patient, who presented with neurological symptoms caused by severe hypoelectrolytemia and metabolic alkalosis. As presented by neurological symptoms and cerebral edema, we suppose that they could be the consequence of severe electrolyte imbalance and alkalosis caused by sweating and vomiting, including the reduction in the plasma concentration of ionized calcium, but not done at the admission [4]. The gradual development of hypoelectrolytemia and metabolic alkalosis with mild dehydration in our patient is not uncommon as reported in other cases with less expressive or even absent signs of dehydration [5]. Dehydration, electrolyte imbalance, and metabolic alkalosis, as a presenting manifestation of CF is relatively common occurring in up to 12 or 16% of patients with CF, may occur in infancy, and are mostly manifested during the summertime [6-8]. In adults, metabolic alkalosis contributes to hypercapnic respiratory failure with acute exacerbation of CF [9]. In countries without neonatal screening for CF, unrecognized cases and atypical presentations are not uncommon including life treating situations with hematological abnormalities [10], intracerebral hemorrhage, and permanent neurological sequelae [11]. Sweat test as a simple, non-invasive method should be frequently performed early in childhood to exclude CF in any suspicious case. Obligatory genetic testing definitely confirms the diagnosis of CF enables to define genotype/phenotype correlations of the specific mutations and has prognostic implications. The most common mutation in the CFTR gene is ΔF508 and accounts for almost 70% of CF patients worldwide [3], in Croatia it accounts 64, 5 % [12].

Homozygous ΔF508 mutation is associated with a classic form of the disease (Up to date 1), with involvement of multiple organs (pancreas, respiratory tract, male reproduction tract) (Up to date 2), and elevated sweat chloride level, electrolytes disbalance [13]. Homozygous ΔF508 is associated with a more severe phenotype and greater risks of morbidity and mortality [3]. The genotype of our patient was Δ F508/ΔF508; 9T/9T. The 9T refers to the polythymidine sequence of intron 8, which is polymorphic with sequences 5, 7 and 9 thymidines. 9T variant allows normal reading of the gene [14] with a found correlation between the number of unaffected transcripts and the severity of lung disease in patients with CF [15].

Farrell [2] in his commentary on the "Early diagnose in New era of CF care" considers that CF should be diagnosed by 2 months of age with a newborn screening program. The early diagnosis enables the clinicians not only to prevent

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malnutrition, chronic *Pseudomonas aeruginosa* infections but gives the opportunity to plan more appropriate treatment [2]. The changing strategy from the "intervention in individuals with illness to prevention in presymptomatic populations" [2] is justified and based on ethical principles strongly supporting the inclusion of CF in newborn screening [2].

Studies from US and UK report significant cost saving from newborn screening in comparison with clinical diagnosis and more cost-effective than many other public health screening programs [16] .

By presenting our case of unrecognised life threatening neurological symptoms caused by the atypical presentation of CF, our intention is not only to argue for inclusion of CF in newborn screening programme but to inform primary care physicians and pediatricians about CF in general, especially about uncommon and life treating presentations.

Based on reports from 27 EU countries, CF is a common inherited disease with a reported mean prevalence of 0.737/10,000 children [2]. In our country, registration for CF started in the year 2007 [17]. Based on collected data, in Croatia, there were 108 CF patients registered in the year 2007 and 122 patients were registered in 2008. According to those data the prevalence of 0.291/10000 children [17] in comparison with the mean prevalence from EU countries [2], CF is still underdiagnosed in Croatia.

In many EU countries, CF is not implemented in the newborn screening programme, including our country. In countries without newborn screening for CF, there is a greater risk of delayed diagnosis with all consequences and possible greater mortality risks. Therefore, implementing CF (besides fenilketonuria and hypothyrosis) in newborn screening programs is justified in Croatia based on medical, bioethical, and economical facts.

We will answer by quoting Andrija Štampar words from 1919 year: "Health budget will not only help the sick but will be use on preventive lines for the benefit on human material on which the nation attention will be focused " [18]. Almost hundred years after Andrija Štampar, we have incredible technological opportunities in medicine but we are still hoping for more preventive lines in the health care budget and we still "have understood only of inorganic capital and know nothing about human capital" [18].

NBS for CF is a preventive procedure that respects the child's health as human capital, saves a life, prevents and postpone complication, and approves the quality of life of patients with CF. Therefore expanding NBS for CF in Croatia is justified based on medical, bioethical, and economical facts.

Conclusion

In Croatia, the data of the incidence and prevalence of CF are still incomplete as the register for CF started in 2007. Newborn screening for CF has not been implemented in a neonatal screening program in many countries, nor in Croatia.

By reporting a case of a 7-month-old boy who's presenting signs of CF were life-threatening neurological symptoms caused by severe metabolic alkalosis and hypoelectrolytemia, we argue hoping to persuade the authorities that implementing CF in newborn screening is cost beneficial in preventing life treating situations with the impact on long-term prognosis of this chronic disease.

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