The Importance of Regular Follow-Up in Children With Cystic Fibrosis And Evaluation Of İnformation About Immunoreactive Trypsinogen İn Screening: A Case Report

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ABSTRACT

OBJECTIVE:

In this study, the importance of follow-up in cystic fibrosis (CF) patients was discussed and information was evaluated about immune reactive trypsinogen (IRT) used in screening. In addition, CF should be keep in mind as a differential diagnosis in patients presenting with pseudo-bartter syndrome (PBS).

CASE: This study included two cases. The first case had normal IRT test in the newborn period. The patient presented to us with diarrhea and vomiting at the age of 3 months and was re-screened for CF, due to presence of PBS. He was diagnosed as CF despite normal screening in the neonatal period. In the second case, we investigated a patient who had CF in the neonatal screening, was not followed up by her family, then came to the hospital with the complaint of malnutrition and was diagnosed with CF at 6 months of age.

CONCLUSION:

There may be cases in which the IRT is misleading during neonatal screening. False negative result may have a probability. Although the screening test is positive, delayed diagnosis of CF may cause many complications in the later years of the patient's life.

Keywords: *Cystic Fibrosis, Genetic Diseases, Newborn Screening*

ÖZET

AMAÇ:

Bu çalışmada, kistik fibrozis (KF) hastalarında takibin önemi tartışılmış ve taramada kullanılan immün reaktif tripsinojen (IRT) hakkında bilgi değerlendirmesinde bulunulmuştur. Ayrıca, pseudo-bartter sendromu (PBS) ile başvuran hastalarda KF'nin ayırıcı tanı olarak akılda tutulması gerektiği belirtilmiştir.

OLGU:

Bu çalışma iki olgu içermektedir. İlk olgunun yenidoğan döneminde yapılan IRT testi normaldi. Hasta bize 3 aylıkken ishal ve kusma ile başvurdu ve PBS varlığı nedeniyle KF için tekrar tarandı. Yenidoğan dönemindeki normal taramaya rağmen KF tanısı aldı. İkinci olguda yenidoğan taramasında KF tespit edilen fakat ailesi tarafından takip edilmeyen, daha sonra yetersiz beslenme şikayeti ile hastaneye gelen ve 6 aylıkken KF teşhisi konan bir hasta araştırılmıştır.

SONUÇ:
Yenidoğan taraması sırasında IRT'nin yanıltıcı olduğu durumlar olabilir. Yanlış negatiflik her zaman göz önünde bulundurulmalıdır. Tarama testi pozitif olsa da geç konulan KF tanısı hastanın yaşamının sonraki yıllarında birçok komplikasyona neden olabilir.

INTRODUCTION
Cystic fibrosis (CF) is an multisystemic and autosomal recessive inherited disease. It is an important cause of severe chronic lung disease and exocrine pancreatic insufficiency in children. In addition, hyponatremic events are seen in many cases (1). Pseudo-Bartter syndrome (PBS) is likely to be associated with attacks of hyponatremic hypochloremic dehydration with metabolic alkalosis in infants with CF. Screening program for CF has been started since 2015 in Turkey (2), but immunoreactive trypsinogen (IRT) may be misleading for screening. The possibility of false negativity should not be ignored (3).

CASE 1
A 3 months old male patient was brought to our hospital for diarrhea and vomiting for the last 4 days. It has been learned that his nutrition has decreased. There was no pathology related to birth and no kinship between his parents. One of the siblings had a diagnosis of CF. The first IRT test performed in the neonatal period was 46.4 ng/mL and the second was 63.2 ng/mL. In physicial examination, patient's height and weight were under 3 percentile. Skin turgor was reduced and sluggish. Systemic examination was normal. Laboratory examination revealed hypokalemia (2.7 mmol/L), hyponatremia (123 mmol/L), hypochloremia (53 mmol/L), and metabolic alkalosis (table 1). There was no growth in sputum and throat culture. The patient's general condition improved with intravenous antibiotic and fluid-electrolyte replacement. His metabolic alkalosis returned to normal on the 5th day of hospitalization. Because of the clinical picture of hypokalemic hypochloremic metabolic alkalosis, vomiting and history of CF in his sibling, CF/PBS was considered. Sweat test was 81 mmol/L.
The patient was accepted as CF and PBS with these findings. In the gene analysis of the patient, homozygous delF508 was detected in CFTR gene mutation and CF diagnosis was confirmed. The patient is now 4 years old, and height-weight percentiles were between 50-75p. He has never had any episodes of PBS since CF was diagnosed.

CASE 2
A 6 months old female patient’s IRT test in the neonatal screening was 268 ng/mL and the second was 322 ng/mL. The sweat test of the patient was 72 mmol/L and she was considered CF but she was not followed up by her family. There was no pathology related to birth. There was a first degree kinship between his parents. One of the siblings had CF. In physicial examination, patient's height and weight were under 3 percentile. When he was brought to our hospital, he had no active complaints and his physical examination was normal. Laboratory examination was unremarkable (table 1). There was no growth in sputum and throat culture. Sweat test was 91.6 mmol/L. CFTR gene analysis revealed homozygous delF508 and the diagnosis of CF was confirmed. The patient is now 3 years old, height-weight percentiles were between 25-50p.

DISCUSSION
Most CF infants with acid-base and electrolyte disorders are likely to have vomiting attacks before admission (4). The first case was a 3 months old male infant who presented with diarrhea and vomiting in the last days. Therefore, PBS should be considered in the differential diagnosis

of infants presenting with hypochloremic metabolic alkalosis and CF should be investigated as an underlying disease. It should be kept in mind that PBS may be the first sign of CF.
Newborns with CF usually have elevations in blood trypsinogen. CF is rare in patients with normal sweat test results, but is likely to be missed (1). IRT results threshold in Turkey is higher than 70 mmol/L. If it is found high with double check, it is directed to the sweat test center. The sweat test (sweat chloride concentration) is referred to as the gold standard. If the measurement results are ≥ 60 mmol/L, CF strongly supports the diagnosis. In this case, gene mutation analysis is performed (5). The fact that the neonatal IRT level is lower than the cut-off value doesn't always mean CF exclusion (6). In a study by Padoan et al, 7.6% false negativity was detected in CF screening (7). In the first case, the patient was diagnosed late because of normal screening. Newborns diagnosed for CF should receive an assessment at the CF center. Genetic counseling should be provided to parents after identification of CF mutation. A newborn with an uncertain diagnosis for CF is not suitable for long-term disease applications. During follow-up, the primary care physician should be informed about the characteristics of clinical management and should work in cooperation with the CF center. Follow-up visits should be made at 3, 6 and 12 months and then annually (8).
Although the second patient's screening test was positive, delayed CF diagnosis may lead to unnecessary hospitalization, development of many complications and burden on public health. Children who can't be diagnosed, whose sweat test is intermediate and who have high IRT screening should be followed for 2 years for signs of CF and the family is informed about what these findings are. In conclusion, being aware of the symptoms of CF, necessary tests for early diagnosis and orient to advanced clinics will have many advantages.

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TABLE 1: Laboratory findings at the time of hospitalization of case 1

WBC g/dL	PLT mm³	Hb g/dL	Na mmol/L	K mmol/L	Cl mmol/L	CRP mg/dl	Ca mg/dL	Mg mg/dL	Alb g/dL	Ph	pCO_2 mmHg	HCO_3 mmol/L
12.500	585.000	11.4	123	2.7	53	<2	10.8	1.4	5.4	7.68	56.7	43.8
Laboratory findings at the time of hospitalization of case 2												
WBC g/dL	PLT mm³	Hb g/dL	Na mmol/L	K mmol/L	Cl mmol/L	CRP mg/dl	Ca mg/dL	Mg mg/dL	Alb g/dL	Ph	pCO_2 mmHg	HCO_3 mmol/L
14.500	605.000	9.3	137	5	107	4.3	9.53	2.21	3.7	7.27	36.6	16.5