The use of sweat chloride test for screening cystic fibrosis among malnourished children suffering from frequent respiratory infections

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ABSTRACT

الأهداف: لإيجاد معيار مسحي فعال ومجدي ماديا لتشخيص التليف الكيسي عند الأطفال (CF) ناقصي الوزن و الذين يعانون من الالتهابات التنفسية المتكررة اعتمادا على فحص التعرق (SCT).

الطريقة: تم إجراء دراسة مسحية ما بين يناير و ديسمبر من عام 2008، وتضمنت 145طفل راجعوا دائرة الأطفال في مستشفى الأمير راشد بن الحسن – مدينة اربد– شمال الأردن و يعانون من التهابات صدرية متكررة وتتراوح أعمارهم من 2 إلى 12 عام (87 ذكور و58 إناث). تم تشخيص 11 منهم بالتليف الكيسي اعتمادا على الفحص الجيني بطريقة تفاعل سلسلة الخمائر الناقلة (PCR)، و134 طفل تم نفي وجود التليف الكيسي CF جينيا لديهم وذلك بالرجوع إلى سجلات المختبر. تم تقييم الطول والوزن بالنسبة للعمرللاطفال الذين تم تشخيصهم بالجينات. وباستخدام التحليل الإحصائي لإيجاد أفضل قيمه منحنى لفحص التعرق SCT للكشف عن التليف الكيسي CF.

النتائج: كانت قيمة فحص التعرقSCT أكثر 57 ملمول/لتر. حساسية تشخيص حالات التليف الكيسي من أول قياس حساسية 100% (95%CI:71.3–100%) وحساسية فحص التعرق SCT لنفي التليف الكيسي المحدد 90.3% (95%CI:84–94.7%). وفحص القبول Kappa test 58.5% كان جيدا.

خاتمة: إذا كانت نتيجة فحص التعرق SCT أكثر من 57 ملمول/لتر فإنها ترجح أكثر الإصابة بالتليف الكيسي، ويجب هذه الحالة عمل فحوصات متقدمة أكثر خصوصا عند الأطفال الذين يعانون من التهابات تنفسية متكررة أوفشل في النمو.

Objectives: To establish a reliable cost-effective screening criterion for cystic fibrosis (CF) among underweight children suffering from frequent chest infections using the sweat chloride test (SCT).

Methods: In a cross-sectional study, 145 children with frequent chest infections were seen in the Pediatric Department at Prince Rashed Bin Al-Hassan Hospital, Irbid, Jordan, between January and December 2008. Their age ranged from 2-12 years (87 males and 58 females). We obtained 11 children with positive polymerase chain reaction (PCR) for CF from hospital laboratory records, and 134 had no confirmed CF. Nutritional anthropometric assessment of weight-for-age and height-for-age based on the Centers for Disease Control and Prevention/World Health Organization 2000 was performed only on the confirmed 11 cases of CF. We used receiver operating curve statistical analysis to find the best SCT cut-off value for screening CF.

Results: The identification of CF is highly sensitive and specific when using the SCT >57 mmol/L. The sensitivity was 100% (95% confidence interval; 71.3-100%), specificity was 90.3% (95% confidence interval; 84-94.7%), and the good reliability Kappa statistical agreement beyond chance was 58.5%.

Conclusion: A sweat chloride result of >57 mmol/L seems to strongly suggest the likelihood of CF, and should trigger further investigation in patients who have frequent respiratory symptoms and have failed to thrive.

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Cystic fibrosis (CF) is the most common lethal inherited autosomal recessive multi-system disorder in Caucasians, it occurs in approximately one of 2500 live births and a carrier frequency of one in 25-30 of the population,[1-5] and has been detected in 39 per 100,000 Jordanian neonates.[6] The inherited CF gene mutation directs the epithelial cells that line many organs (including the lungs, liver, pancreas, digestive tract, reproductive tract, skin, and sweat glands) to produce a defective form of a protein called a CF transmembrane conductance regulator (CFTR), and then the epithelial cells cannot regulate the way chloride passes across cell membranes. This leads to disruption of salt and water balance needed to maintain a thin coating of fluid and mucus inside different organs. The resultant thick and sticky mucous is hard to move, which makes it liable to infection in the lungs that causes it to block the channels that would normally carry important enzymes from the pancreas to the intestines to help digest food. This results in poor absorption of different nutrients, especially fats.[3,4,7-11] Thus, children with CF do not gain weight as expected and fail to thrive despite having a normal diet and good appetite. The inability of these children to properly digest and absorb proteins and fats make their stool oily and bulky and put them at risk of deficiencies in the fat-soluble vitamins (vitamins A, D, E, and K). Unabsorbed fats may also cause excessive intestinal gas, an abnormally swollen belly, and abdominal pain, or discomfort.[5,12-14] The sweat chloride test (SCT) is ordered when a patient has symptoms suggestively of CF that includes noticeably salty sweat, frequent respiratory infections and chronic cough, gastrointestinal symptoms, distal intestinal obstruction (meconium ileus in infants), bulky offensive greasy stools (steatorrhea), and malnutrition.[15-20]

Our goal in this study is to estimate the best sweat chloride concentration cut-off value by using the Macroduct sweat collector (WESCOR Inc., Utah, USA) for screening CF among children suffering from recurrent respiratory infections and who had been registered at Prince Rashed Bin Al-Hassan Hospital Laboratory, Irbid, Jordan and had been diagnosed definitively by the polymerase chain reaction (PCR) at Princess Eman Research and laboratory Sciences Center with the goal of introducing early cost-effective primary health care.

Methods. From January to December 2008, 145 children with suspected CF were seen at the pediatric department. The age range was 2-12 years (87 males and 58 females). The local ethics committee approved the study. All these patients have available laboratory records for SCTs and PCR. Inclusion criteria include: salty sweat, frequent respiratory infections, chronic cough and signs of malnutrition. Sweat chloride test using the Wescor Macroduct collecting system was performed on the selected patients at Prince Rashed Bin Al-Hassan Military Hospital Laboratory, Irbid, Jordan. Subsequently, the PCR was performed at a more sophisticated laboratory in Princess Eman Research and Laboratory Sciences Center, Amman, Jordan on selected patients for definitive diagnosis.

The SCT was carried out in 3 phases: 1) induction of sweating by pilocarpine iontophoresis for 30-60 seconds. 2) The Macroduct collecting system (**Figure 1**) was tightly placed on the forearm for half an hour. 3) Chloride was measured by biochemical electrolyte device (sweat conductivity Analyzer (WESCOR Inc., Utah, USA). The patients were divided into 2 study groups: Group I: included 11 children with CF (positive PCR for CF). Group II: included 134 children with no CF confirmed by PCR.

The collected data included age, gender, and sweat chloride concentration. The measurement of individual anthropometric nutritional assessment was performed by Epi Info version 3.4.3 for the 11 cases of definitive CF diagnosed by PCR when they were seen at the Primary Health care clinic and had been vaccinated by influenza. These measurements were based on the CDC/WHO 2000 child growth standards of height-for-age and weight-for-age percentiles. Data were recorded and analyzed using a Statistical Package of Social Science version 15 and MedCalc version 9.3.0.0 computer based program. We used cross-tabulation, mean comparison, and receiver operating curve (ROC) analysis to find the best sweat chloride concentration cut-off value for screening CF. A p-value of <0.05 was considered significant. The Kappa reliability statistical test that measured the agreement beyond chance was used. The Kappa agreement values were: <0 means less chance agreement, 1-20% slight agreement, 21-40% fair agreement, 41-60% good agreement, 61-80% substantial agreement, and 81-99% almost perfect agreement.[21]

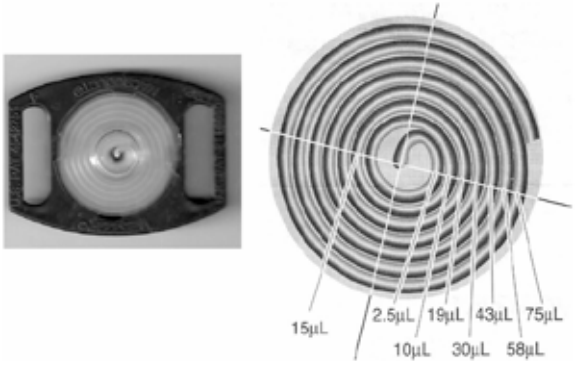

Figure 1 - Macroduct collecting system.

Table 1 - The demographic characteristics, anthropometric and comparison of age, gender, sweat chloride concentration between positive and negative polymerase chain reaction (PCR) for definitive diagnosis of cystic fibrosis (CF).

Demographic characteristics	Positive PCR for CF	Negative PCR for CF	*P*-value
n (%)	11 (7.6)	134 (92.4)	
Age (years)	6.6 ± 2.5	5.9 ± 2.6	0.392
Gender (M/F)	6/5	81/52	0.679
Height cm (mean ± SD)	109.5 ± 14.3	-	-
Weight per kg (mean ± SD)	19.1 ± 7.8	-	-
Sweat chloride concentration/mmol/L (mean ± SD)	77.4 ± 16.9	41.6 ± 15.2	<0.0001

Table 2 - Age, gender, and nutritional status for patients with positive polymerase chain reaction for cystic fibrosis.

Age (years)	Gender	Weight-for-age percentile	Height-for-age percentile
6	M	0.5 (below 3rd percentile)	0.25 (below 3rd percentile)
3	M	0.51 (below 3rd percentile)	4.61 (below 5th percentile)
8	M	1.84 (below 3rd percentile)	2.41 (below 3rd Percentile)
8.5	F	0.93 (below 3rd percentile)	12.11 (above 5th percentile)
5	F	2.36 (below 3rd percentile)	12.4 (above 5th percentile)
8	M	0.25 (below 3rd percentile)	1.7 (below 3rd percentile)
12	F	2.23 (below 3rd percentile)	2.91 (below 3rd percentile)
7	F	2.36 (below 3rd percentile)	1.96 (below 3rd percentile)
5	F	28.26 (above 5th percentile)	50.51 (above 5th percentile)
7	M	2.01 (below 3rd percentile)	4.23 (below 5th percentile)
6	M	0.78 (below 3rd percentile)	2.46 (below 3rd percentile)
6.6 ± 2.5*		3.8 ± 8.1*	8.7 ± 14.4*

*mean±SD

Results. The age range of the patients was 2-12 years, there was no difference between the age of CF cases and the age of the children without CF (p=0.392) (**Table 1**). There was no difference between males and females, and the results obtained were not divided according to gender (p=0.679). A statistically significant difference of sweat chloride concentration (mmol/L) was noted in the positive PCR CF group when compared with the negative PCR CF group (p<0.0001) (**Table 1**).

Table 2 shows the nutritional status as indicated by the WHO 2000 child growth standards for 11 cases with definitive CF. The weight-for-age of 11 cases is less than the third percentile, which means that all CF cases were wasted and failed to gain weight (underweight). Six out of 11 cases of CF showed height-for-age less than third percentile (stunted; linear growth). However, 8 out of 11 CF cases showed height for age less than fifth percentile and they were considered as failure to thrive.

Table 3 and **Figure 2** show the identification of CF to be highly sensitive and specific, whenever using sweat chloride concentration >57 mmol/L. The sensitivity was 100%, specificity 90.3% and good reliability Kappa statistical agreement beyond chance was 58.5%. The most common mutations identified are summarized in **Table 4**.

Discussion. In this study, 145 children were referred to the pediatric department for various respiratory manifestations through the year 2008. We were able to identify 11 children with positive PCR for CF with high

Table 3 - The best sweat chloride concentration, cutoff value to find CF cases, sensitivity, specificity and agreement beyond chance (Kappa test).

Sweat chloride concentration	Positive PCR for CF	Negative PCR for CF	Sensitivity % and 95% CI	Specificity % and 95% CI	Kappa%
>57 mmol/L	11	13	100 (71.3 – 100)	90.3 (84.0-94.7)	58.5
≤57 mmol/L	0	121			

Kappa statistic which measure agreement beyond chance. CI - confidence interval

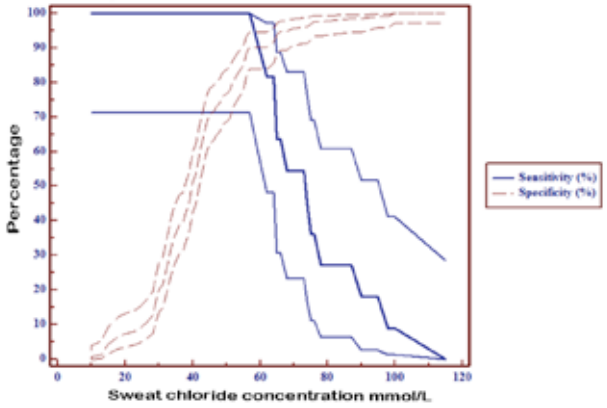

Figure 2 - Sensitivity and specificity distribution points of sweat chloride concentrations for screening of cystic fibrosis.

values of sweat chloride concentration compared with 134 children with a negative PCR for CF. Therefore, this study, which is directed by ROC curve analysis, finds that the sweat chloride concentration cut-off value of >57 mmol/L was the most reliable in identifying cases of CF. This result is somewhat consistent with other studies that adopted similar cut-off values for the sweat chloride concentration. This may be directly related to the CFTR protein activity, as the chloride channel is dependent on cyclic AMP (cAMP).[22-29] The sweat chloride concentration test is the primary test for diagnosing CF,[25,30] and the normal individual has sweat chloride concentrations <50 mmol/L.[25,31,32] In this study, the CF frequency is equal among males and females, due to its inherited autosomal recessive disorder.[2,4,31-34] This means that males and females are equally likely to be affected and both parents might be the carrier of CF gene to have an affected child.[35-42] The study showed that children with CF have difficulty gaining weight and have less than ideal body weight and height. Multiple factors influence the nutritional status of patients with CF, including pancreatic exocrine dysfunction that causes maldigestion characterized by failure to thrive, genotype, diet, eating behavior, nutritional supplements, severity of lung disease, and possible age at the time of diagnosis.[18,19,36,43-46] The most common mutations identified in this study were F508/unidentified, W1282X/unidentified, F508/F508,

Table 4 - The frequency of observed genotypes for 11 positive polymerase chain reaction for cystic fibrosis.

Genotype	No. of patients (%)
F508/unidentified	4 (36.4)
W1282X/unidentified	3 (27.3)
F508/F508	2 (18.2)
F508/W1282X	2 (18.2)
Total	**11 (100)**

and F508/W1282X, somewhat consistent with another study in North Jordan.[47]

Limitations of the present study include the restricted sampling of children holding military health insurance referred to the Pediatric Department at Prince Rashed Bin Al-Hassan Military Hospital in the North of Jordan where the study was conducted because of frequent chest infections. Therefore, the sample may not be enough to represent the whole population. Moreover, we did not study the socio-economic, demographic, and racial differences that may affect the occurrence of CF. The investigations by PCR were performed at a more sophisticated laboratory in Princess Eman Research and Laboratory Sciences Center in Amman, Jordan and were limited to the most common gene mutations in our region. Therefore, it is possible that not all subjects with CF were diagnosed. The screening based on the SCT in younger babies may not produce enough sweat to give reliable test results and may need to be repeated. It also does not determine the severity of symptoms. However, our study was carried out for the best-estimated SCT cut-off value for screening CF in a limited sample in North of Jordan despite the severity of CF, and it must have detected the great majority of cases.

In conclusion, the sweat chloride concentration test by Wescor Macroduct collecting system is a useful tool for the prediction of patients with CF at the primary care level where the resources are limited. A sweat chloride result of >57 mmol/L seems to predict a better likelihood of CF, and should trigger further investigation in those patients who have frequent respiratory symptoms, steatorrhea, abdominal pain, and malnutrition evidenced by wasting and stunting.

Therefore, the developing primary health care strategies are essential for early diagnosis, control, management, and prevention of further complications.

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