Malays J Pathol 2020; 42(2): 297 – 300

CASE REPORT

The role of biochemical testing in cystic fibrosis

Faridatul Husna ABDUL RAHIM[1,2], Subashini C. THAMBIAH[1]*, Intan Nureslyna SAMSUDIN[1], Normaizuwana MOHAMED MOKHTAR[2]

[1]Department of Pathology, Faculty of Medicine and Health Science, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia. and [2]Department of Pathology, Hospital Kuala Lumpur, Jalan Pahang, 53000 Kuala Lumpur, Malaysia.

Abstract

Introduction: Cystic fibrosis (CF) is a life-limiting autosomal recessive disorder as a result of CF transmembrane conductance regulator gene mutation. It has a wide range of disease severity in patients with the same genotype. *Case report*: A 5-year-old Malay boy with a history of recurrent pneumonia, presented with productive cough, fever and worsening tachypnoea. Physical examination revealed coarse crepitations, reduced breath sounds and clubbing. Biochemical investigations showed that he had respiratory type 2 failure as a result of bronchiectasis. Sweat conductivity done twice was raised supporting a diagnosis of CF. Other investigations such as bronchoscopy to look for congenital anomaly of the lung, infectious disease screening and tuberculosis, fungal and viral culture and sensitivity were negative. Further cascade screening revealed high sweat conductivity results in his siblings. *Discussion*: Although CF prevalence is low in Malaysia, it is nevertheless an important diagnosis to be recognised as it is associated with increased morbidity.

Keywords: Cystic fibrosis, sweat chloride test, sweat conductivity, cystic fibrosis transmembrane conductance regulator gene mutation, cascade screening

INTRODUCTION

Cystic fibrosis (CF) is a life-limiting autosomal recessive disorder as a result of CF transmembrane conductance regulator (*CFTR*) gene mutation.[1] We report a case of typical CF features in a 5-year-old Malay boy that was diagnosed following high sweat conductivity results after several investigations were done to rule out more common causes of bronchiectasis.

CASE REPORT

A 5-year-old Malay boy with a history of recurrent pneumonia, presented with productive cough, fever and worsening tachypnoea over 3 days. His first admission was at 3 months old in a district hospital and he was repeatedly admitted 3 to 4 monthly for the same problem. At 3 years old, he was readmitted for pneumonia secondary to *Pseudomonas aeruginosa* infection. After 2 months, he was admitted again for a similar presentation and contrast-enhanced computed tomography thorax showed bronchiectatic changes. However, he defaulted follow up until this presentation.

Physical examination revealed he was small for age below the 3rd percentile consistent with failure to thrive, cachexic and had clubbing of his fingers and toes. On examination, he was tachycardic and tachypnoeic with presence of chest recession. He had a hyperinflated chest and pectus carinatum. On auscultation, there were generalised coarse crepitations with prolonged expiratory phase and rhonchi. He was treated with frequent nebuliser and antibiotics. Sputum culture and sensitivity (C&S) showed *Pseudomonas aeruginosa* infection. He was then referred to a respiratory paediatrician in a tertiary hospital for further investigation and management in view of recurrent pneumonia with bronchiectasis.

On admission at the tertiary hospital, he had persistently low oxygen saturation at 90% under room air and required oxygen support. A positive sweat conductivity of more than 80 mmol/L (> 80 mmol/L) supported the diagnosis of CF in this patient. His stool for fat globule was negative. Other investigations such as

**Address for correspondence*: Associate Professor Dr. Subashini Chellappah Thambiah, Department of Pathology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia. Tel: +60123923709, Fax: 03-97692373, Email: *subashini@upm.edu.my*

bronchoscopy to look for congenital anomaly of the lung, infectious screening and tuberculosis, fungal and viral C&S were negative.

He is the third among 4 children from a non-consanguineous marriage. Both parents are of Malay ethnicity and reported as healthy. The elder and younger brothers who were 10 and 2 years old, respectively also had a history of recurrent pneumonia due to pseudomonas infection. His 7-year-old sister was asymptomatic. Cascade screening revealed high sweat conductivity (> 80 mmol/L) results in all his siblings. Sweat conductivity was, however, not performed for his parents.

DISCUSSION

Epidemiology

CF varies according to race and ethnicity, common among Caucasians with low incidence rates in Malaysia.[2] In Malaysia, 16 and 12 patients were confirmed to have CF from the year 1987 to 2003[3] and from 2000 to 2009[2], respectively.

Clinical features and complications

This patient presented with recurrent pseudomonas pneumonia with consequent bronchiectasis and failure to thrive, which are typical CF respiratory features. He had no evidence of gastrointestinal features of CF such as malabsorption or obstructive symptoms.

Pathophysiology

CFTR protein and genetic mutations

CF is caused by gene mutations in *CFTR* on the long arm of chromosome 7. *CFTR* mutations can reduce channel number, function or both, and can vary in severity and occur through a variety of cellular mechanisms. The most common *CFTR* allele mutation is the deletion of phenylalanine at position 508. The relative severity and completeness of each genetic defect has a major influence on the manifestations and the severity of the disease, although genetic modifiers and environmental factors also have a role.[4]

This patient already had respiratory symptoms since he was 3 months old and was diagnosed to have bronchiectasis at the age of 5. Furthermore, he presented with pulmonary symptoms at an early age.[1] However, he had no history of gastrointestinal symptoms suggestive of pancreatic insufficiency such as meconium ileus, chronic diarrhoea or evidence of vitamin A, D, E or K deficiencies and no fat malabsorption as stool for fat globule was negative. This shows that he may either have 2 non-functional CFTR alleles or that he has one CFTR allele that is partially active preserving his pancreatic function.[1] The other possibility is that he may have one functional CFTR allele combined with a non-functional CFTR allele but due to the presence of genetic modifiers and environmental factors, his phenotypic lung disease is severe.[4]

Surprisingly, his elder sister was asymptomatic despite having high sweat conductivity. This could be due to preanalytical error during sweat collection such as contamination of the skin with topical anaesthetic gel or saline that contains sodium chloride or presence of dermatitis at the sweat collection area,[5] which was excluded in her. As in this case, if the preanalytical step has been optimised, it is best to confirm the diagnosis by sweat chloride test or genetic analysis testing.[6] The genetic analysis testing for the elder sister may reveal a single allele with no functional CFTR combined with one allele that has sufficient function. As she is currently asymptomatic, there is also a possibility that she has 2 mild or variable mutations; although she may present with CF symptoms later in life.[1]

Airway pathophysiology in CF

Recurrent pneumonia with bronchiectasis in this patient is because of the defect in CFTR that primarily functions as an anion channel of chloride and bicarbonate on epithelial cells. In this patient, defect in CFTR has caused inadequate airway surface liquid resulting in thick mucous with subsequent plug formation. Long term, this plug formation will eventually lead to airway blockage and ineffective mucociliary transport of epithelial airway.[7] Recurrent and persistent pseudomonas infection in this patient is due to abnormal pH regulation of the defective airway defence causing defective bacterial killing, dysfunctional macrophages and abnormal degranulation in neutrophil.[7]

Laboratory investigations (Table 1)

Mild normocytic, normochromic anaemia of chronic disease and raised erythrocyte sedimentation rate (ESR) were due to recurrent pneumonia due to CF and poor nutritional support. Normal electrolyte values and negative stool fat globule excluded malabsorption in this patient. Albumin being a negative acute-phase protein in inflammation was low in this patient. It also reflects the patient's malnourished state.[8] Although his liver function tests (LFT) were normal, the complications of hepatobiliary disease associated with CF such as cirrhosis,

portal hypertension, ascites, bleeding varices usually affect teenagers and adults.[2] As such, it is important to monitor his LFT closely. Arterial blood gas (ABG) showed compensated respiratory acidosis consistent with the patient's current respiratory infection with underlying bronchiectasis. His positive sweat conductivity of > 80 mmol/L supported the diagnosis of CF.

Sweat conductivity test

The sweat chloride test remains the gold standard for CF diagnosis.[6] However, in this patient sweat conductivity was used. Sweat conductivity is measured by comparing electrical conductance of sweat to that of sodium chloride (NaCl) standard solution. It represents the molar concentration of NaCl in the solution that has the same conductivity as the sweat sample and does not represent an actual concentration of sodium or chloride ions in the sweat sample.[9] Sweat conductivity is less expensive compared to sweat chloride test, hence more cost-effective in view of the low prevalence of CF in Malaysia. Besides that, it is a simpler sweat test method that eliminates the weighing and dilution steps in sweat chloride test and reduces the risk of sample

TABLE 1: Laboratory investigations

Test	Result	Reference Interval
HAEMATOLOGY		
Haemoglobin	9.7	(11.3-14.3) g/dL
Total white cell	15.2	(6.5-16) x 10^3/uL
Platelet	502	(200-550) x 10^3/uL
Mean Corpuscular Volume	76	(70-85) fL
Mean Corpuscular Haemoglobin	28	(23-31) pg
Erythrocyte sedimentation rate	105	(<22) mm/hr
BIOCHEMISTRY		
Urea	4.7	(3.2-8.1) mmol/L
Sodium	136	(136-145) mmol/L
Potassium	4.1	(3.5-4.5) mmol/L
Chloride	98	(97-107) mmol/L
Creatinine	29	(25-42) µmol/L
Total protein	82	(64-83) g/L
Albumin	29	(38-54) g/L
Alkaline phosphatase (ALP)	194	(<269) U/L
Alanine transferase (ALT)	24	(<41) U/L
Total bilirubin	3	(<17) umol/L
pH	7.38	7.38-7.45
Partial pressure carbon dioxide(pCO_2)	57.5	(27-39.7) mmHg
Partial pressure oxygen (pO_2)	105	(69.8-86.3) mmHg
Bicarbonate (HCO^-_3)	31.3	(19.8-24.2) mmol/L
Stool for Fat Globule	Negative	Normal: (0-60) mmol/L
Sweat conductivity	84	Borderline: (60-80) mmol/L
Sweat conductivity (repeat)	138	Abnormal: >80 mmol/L
MICROBIOLOGY		
Sputum culture and sensitivity (C&S)	*Pseudomonas aeruginosa*	
Sputum acid fast bacilli (AFB)	Satisfactory, Negative	
Nasopharyngeal aspiration for respiratory viruses	Negative	
Blood C&S	No growth	
Human Immunodeficiency Viral (HIV) serology	Negative	
Hepatitis B & C serology	Negative	
Venereal Disease Research Laboratory (VDRL) Test	Negative	
Treponema Pallidum Serology	Negative	

evaporation.[6] Despite having a good correlation with sweat chloride test, sweat conductivity is still recommended only as a screening test[9] because it does not measure sweat chloride concentration alone but also reflects the concentration of other ions such as lactate and bicarbonate, which bear less or no relation to CFTR function.[9] Hence, the reference values for sweat conductivity in CF patients are approximately 15 mmol/L higher than sweat chloride values. Values higher than 80 mmol/L support a diagnosis of CF.[9] There is lack of uniformity in sweat conductivity testing with regards to the selection criteria of the patient such as age and weight, sample collection, test interpretation, reference intervals used and reporting. This could be due to the limited guidelines available to address these issues. Moreover, there are less studies about limitations of sweat conductivity compared to sweat chloride testing. Thus, standardisation in testing and reporting of sweat conductivity is required.[10]

CONCLUSION

Bronchiectasis is the most common presentation of CF. However, due to the low prevalence of CF in Malaysia, other causes of bronchiectasis as mentioned before were ruled out in this patient. High sweat conductivity in this patient supported the clinical findings of CF. Routine blood investigations such as renal profile, LFT and ABG in this patient helped monitor the complications of CF and ensure optimal management. Since sweat chloride measurement is not available in Malaysia, there is a role for genetic testing in this patient and his siblings to confirm the diagnosis since sweat conductivity is only a screening test. More so for his elder sister who was asymptomatic but showed high result of sweat conductivity.

Acknowledgement: The authors would like to thank the Director General of Health Malaysia for his permission to publish this article.

Conflict of interest: The authors declare they have no conflict of interest.

REFERENCES

1. Weiler CA, Drumm ML. Genetic Influences on Cystic Fibrosis Lung Disease Severity. Front. Pharmacol. 2013; 4: 40.
2. Walters S, Mehta A. Epidemiology of cystic fibrosis. In: Hodson M, Geddes DM, Bush A, editors. Cystic fibrosis, 3rd ed. London: Edward Arnold Ltd; 2007: 21–45.
3. Boeck KD, Derichs N, Fajac I, *et al*. New clinical diagnostic procedures for cystic fibrosis in Europe. J Cyst Fibros. 2011; 10(Suppl 2), S53–S66.
4. O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet. 2009; 373(9678): 1891-904.
5. Guglani L, Sitwat B, Lower D, Kurland G, Weiner DJ. Elevated sweat chloride concentration in children without cystic fibrosis who are receiving topiramate therapy. Pediatr Pulmonol. 2012; 47(5): 429-33.
6. Farrell PM, White TB, Ren CL, *et al*. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017; 181S: S4-S15.e1.
7. Donaldson SH, Boucher RC. Pathophysiology of Cystic Fibrosis. Ann Nestlé. 2006; 64: 101-9.
8. William JM, Stephen KB, Marta L. Water, sodium and potassium. In: Clinical Chemistry. 8th ed. New York: Mosby Elsevier; 2017. p.13-39.
9. Massie J, Greaves R, Metz M, *et al*. Australasian Guideline (2nd Edition): An Annex to the CLSI and UK Guidelines for the Performance of the Sweat Test for the Diagnosis of Cystic Fibrosis. Clin Biochem Rev. 2017; 38(3):115-30.
10. Greaves RF, Jolly L, Massie J, *et al*. Laboratory performance of sweat conductivity for the screening of cystic fibrosis. Clin Chem Lab Med. 2018; 56(4):554-9.