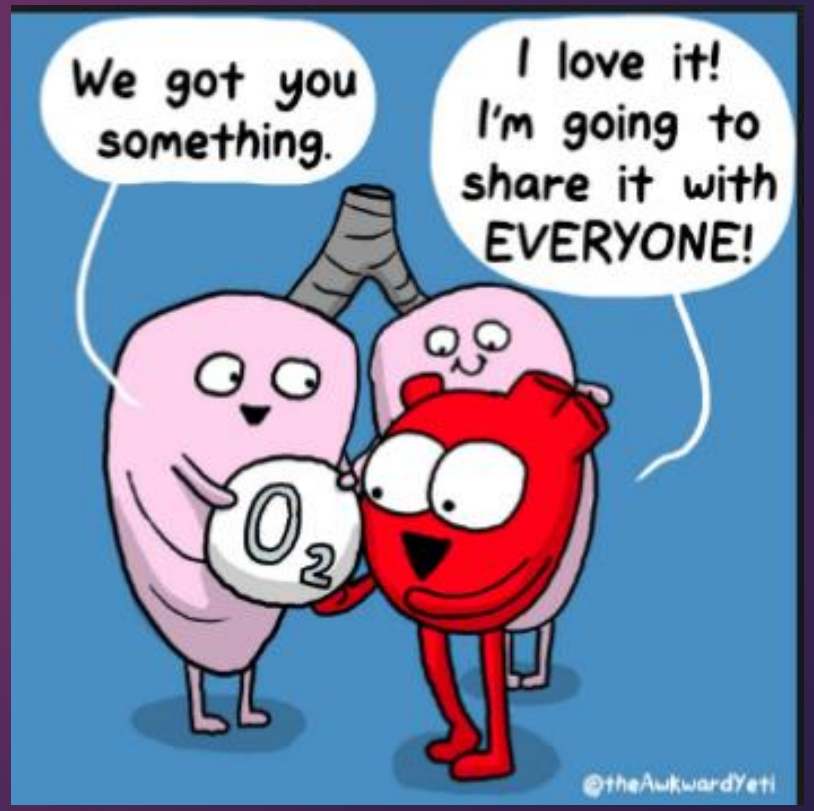
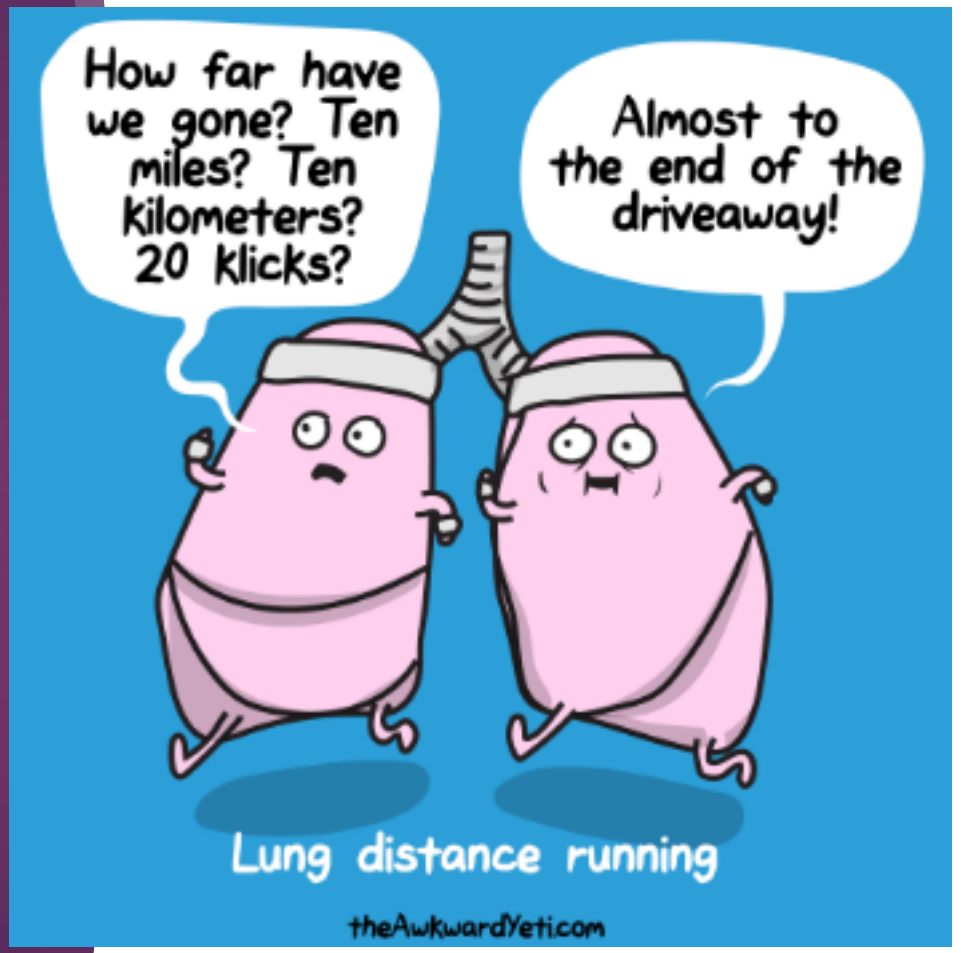
Cross-Canada Rounds



Danielle Adam, PGY5
Pediatric Respirology Fellow
December 20th, 2018

Case


How far have we gone? Ten miles? Ten kilometers? 20 klicks?
Almost to the end of the driveaway!
Lung distance running
theAwkwardYeti.com

Case

- 14yo male: referred for poorly controlled asthma and persistent Xray changes
- Diagnosed at age 3 (recurrent cough and wheezing)
- Previous treatment: Flovent and Symbicort PRN
- Present treatment (for the last year): Zenhale 100mcg 2 puffs BID, Singulair 5mg once daily, and Nasonex, no Ventolin use last year
  - Ventolin has helped in the past

Case

- Present symptoms: chest tightness and SOB with exercise (5min of running)
- Exercises 4 times a week
- Chronic dry cough every night
- Only sick once this winter with a cold
- Previous illnesses: LUL pneumonia – treated with abx with incomplete resolution (persistent x-ray changes). Repeated abx and prednisone

Case: Past Medical History

- Adopted as a baby, no neonatal respiratory distress
- No hospitalizations, surgeries
- Several childhood visit to the ER for asthma and received steroids multiple times (last oral steroids for asthma was 5 years ago)
- Suspected allergies to cats, dogs, dust
- Family history: limited known about biological family except for history of CF

Case: Review of Systems

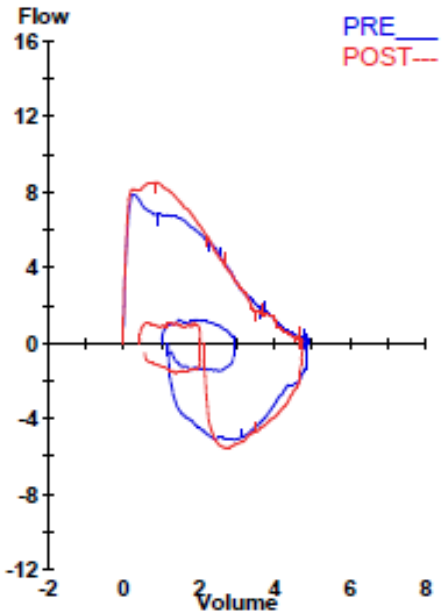
- Chronic nasal congestion, no polyps
- No history of choking or coughing with eating
- Normal bowel movements
- No eczema history
- No snoring
- Growing well
- Multiple ear infections in early childhood but otherwise no history to suggest immunodeficiency

Chest X-Ray

Any additional investigations you want to do?

SPIROMETRY

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
FVC	Liters	4.13	4.88	118	4.76	115	-3
FEV1	Liters	3.81	3.81	100	3.69	97	-3
FEV1/FVC	%	86	78	91	78	90	-1
FEF25-75%	L/sec	4.19	3.32	79	3.26	78	-2
FEF50%	L/sec	4.73	4.56	96	4.45	94	-2
FEF75%	L/sec	2.63	1.57	60	1.38	52	-12
PEF	L/sec	7.91	8.41	106	8.88	112	6
FIVC	Liters		3.70		2.63		-29
PIF	L/sec		5.11		5.56		9
MVV	L/min						



LUNG VOLUMES (PLETHYSMOGRAPHY)

	Ref	Pre Meas	Pre % Ref
VC	4.13	5.19	126
TLC PI	5.27	6.67	127
RV Liters	1.08	1.48	137
RV/TLC %	20	22	108
FRC PL Liters	2.49	3.56	143
IC Liters		3.11	
ERV Liters		2.10	

COMMENTS:

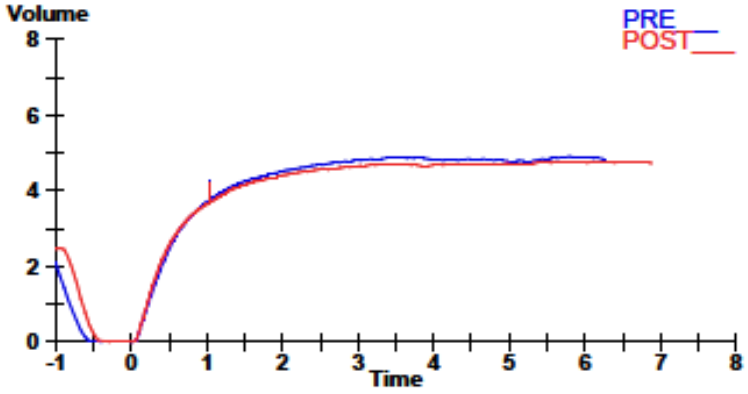
The patient provided good effort, however, was unable to meet end of test criteria for flow volume loops- ATS criteria were not met. Lung volumes and DLCO testing met ATS criteria. 4 puffs of bronchodilator - Salbutamol, were administered via space chamber.

DIFFUSION CAPACITY

		Ref	Pre Meas	Pre % Ref
DLCO	mL/mmHg/min	28.6	28.5	100
DL Adj	mL/mmHg/min	28.6	28.5	100
VA	Liters	5.27	5.70	108
DLCO adj for VA		28.6	27.6	97
IVC	Liters		4.78	

AIRWAYS RESISTANCE

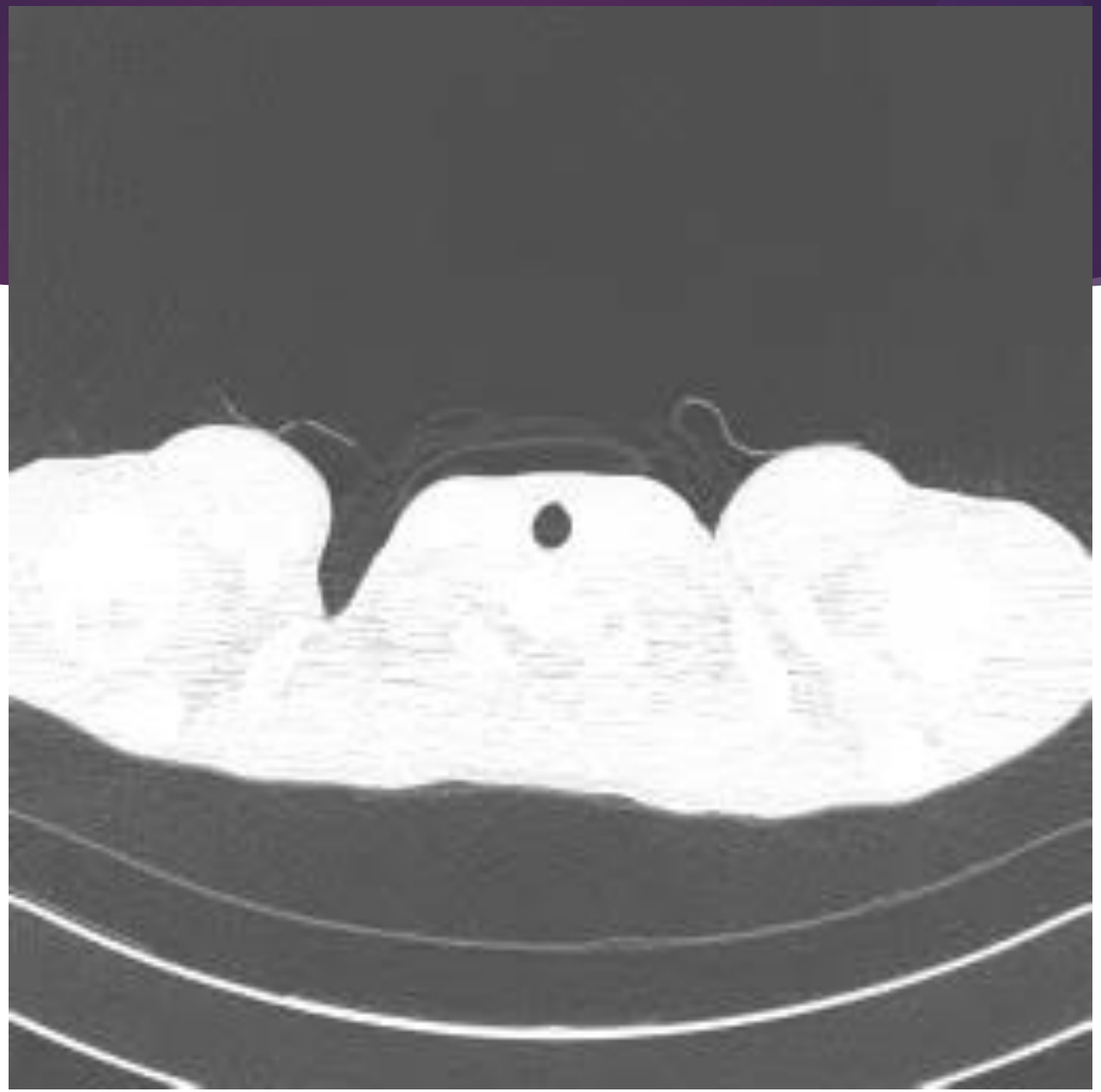
		Ref	Pre Meas	Pre % Ref
Raw	cmH2O/L/sec	2.28		
Gaw	L/sec/cmH2O	0.119		
sRaw	cmH2O/L/s/L	5.97		
sGaw	L/s/cmH2O/L	0.168		
Vtg (Raw)	Liters			



Case: Next steps

- CT
- Allergy test: Positive for horse, trees, indoor and outdoor molds, house dust mites and cat
- CBC: normal

CT

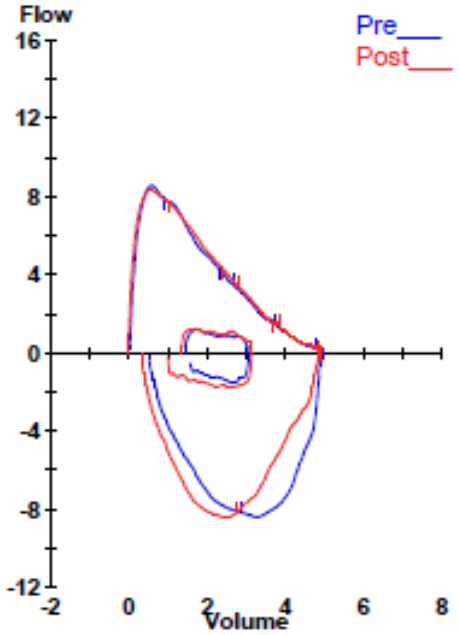


Follow-up

- His Singulair was optimized to 10mg once daily and he as given a Ventolin discus to take with exercise. He was told to remain on the Zenhale
- He returned to clinic 4-6 weeks later and is very happy with the improvement.
- He is now completely asymptomatic

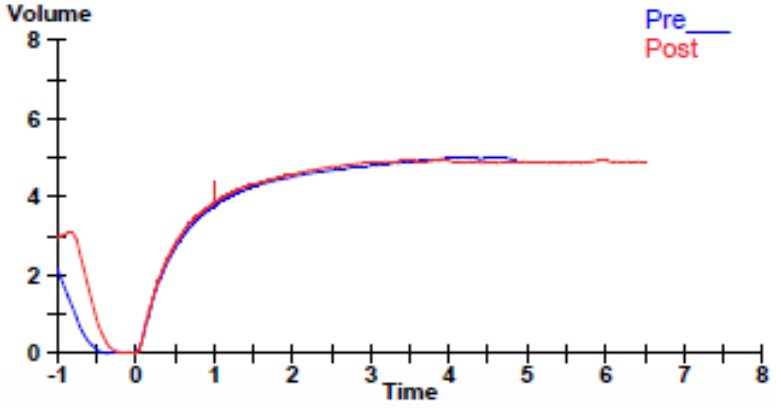
SPIROMETRY

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
FVC	Liters	4.27	4.99	117	4.93	115	-1
FEV1	Liters	3.94	3.78	96	3.89	99	3
FEV1/FVC	%	86	76	88	79	92	4
FEF25-75%	L/sec	4.32	3.10	72	3.51	81	13
FEF50%	L/sec	4.89	3.96	81	4.33	89	9
FEF75%	L/sec	2.74	1.42	52	1.63	59	14
PEF	L/sec	8.14	8.55	105	8.42	103	-2
FET100%	Sec		4.86		6.49		34
FIVC	Liters		4.45		4.58		3
PIF	L/sec		8.39		8.42		0
MVV	L/min						



COMMENTS:

Last used Zenhale approximately 16 hours prior to testing, has not used Ventolin over past month.
4 puffs of bronchodilator - Salbutamol, were administered via space chamber.
The patient provided adequate effort, flow volume loop testing met ATS criteria.



Case – more details

- Sweat chloride: 59 (repeat 58)
- IgE: 8981
- Bronch: lipid laden macrophages, no bacterial growth, scant secretions

Outline

- To review the criteria and suggested workup for difficult to treat asthma.
- To review normal sweat chloride levels, and what it could mean to have an indeterminate sweat chloride level
- To outline the possible relationship of elevated sweat chloride levels and difficult to treat asthma

Difficult to Treat Asthma

- DEFINITION
- WORK-UP
- SWEAT CHLORIDE LINK?

Definition

"Recognition and management of severe asthma: A Canadian Thoracic Society position statement"

Severe asthma

Asthma which requires treatment with high-dose ICS as outlined in Table 1 (adults and children) and a second controller for the previous year, or systemic corticosteroids for 50% of the previous year to prevent it from becoming "uncontrolled", or which remains "uncontrolled" despite this therapy is defined as severe asthma.

Uncontrolled asthma is defined as at least one of the following:

1) Poor symptom control: *as per* Canadian Thoracic Society asthma control criteria* or other standardized questionnaires: Asthma Control Questionnaire (ACQ) consistently > 1.5, Asthma Controlled Test (ACT) <20, or child Asthma Controlled Test (cACT) < 20.
2) Frequent severe exacerbations: two or more courses of systemic corticosteroids (≥3 days each) in the previous year.
3) Serious exacerbations: at least one hospitalization, intensive care unit (ICU) stay or mechanical ventilation in the previous year.
4) Airflow limitation: after appropriate bronchodilator withhold forced expiratory volume in one second (FEV_1) <80% of personal best (or < the lower limit of normal (LLN), in the face of reduced FEV_1/forced vital capacity (FVC) defined as less than the LLN).

*Not meeting the criteria described in Table 2.[5]

CTS Position Statement

- "A diagnosis of asthma using **objective measures**, the assessment of **domestic and work environment** along with the **verification of adherence to medication and co-morbidities** is key"
- Non-adherence to treatment = major challenge
- Another issue: incorrect use of inhalers
- Consider co-morbidities during initial assessment esp if:
  - Lack of response to ICS with another controller
  - Usual management of the most frequent reasons for poor control

A Practical Approach to Severe Asthma in Children

Emily E. Barsky[1,2], Lauren M. Giancola[1], Sachin N. Baxi[2,3], and Jonathan M. Gaffin[1,2]

[1]Division of Respiratory Diseases and [3]Division of Allergy and Immunology, Department of Medicine, Boston Children's Hospital, Boston, Massachusetts; and [2]Harvard Medical School, Boston, Massachusetts

- Step 1: Diagnosis Confirmation
- Step 2: Evaluation and Optimization of Difficult to Treat Asthma
- Step 3: Assessment and Management of Severe Asthma Refractory to Traditional Therapy
- Step 4: Efficacy Assessment

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Step 1: Diagnosis Confirmation

- 30% of referrals for severe asthma = misdiagnosed
- History, physical and spirometry
- Atypical presentations
- Consider: lung volumes, sweat test, bronchoscopy, CT

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Step 2/3: Evaluation and Optimization of Difficult to Treat Asthma & Asthma refractory to traditional therapy

- Adherence, technique and optimizing delivery
- Use of technology
- Environment
- Management (refractory disease)
  - Steroids (oral)
  - Anticholinergics
  - Biologics

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Emerging therapeutic considerations:

- Increased inhaled steroids during exacerbations
- Theophylline
- Additional biologics
- Antimicrobial drugs
- Immunosuppressants
- Allergen immunotherapy
- Surgical Intervention

Sweat Chloride

THE INDETERMINATE LEVEL

IS THERE A LINK TO DTT ASTHMA?

FALSE-POSITIVE
Adrenal insufficiency
Eczema
Ectodermal dysplasia
Nephrogenic diabetes insipidus
Hypothyroidism
Fucosidosis
Mucopolysaccharidosis
Dehydration
Malnutrition
Poor technique/inadequate sweat collection
Type I glycogen storage disease
Panhypopituitarism
Pseudohypoaldosteronism
Hypoparathyroidism
Prostaglandin E_1 administration

FALSE-NEGATIVE
Edema
Poor technique/inadequate sweat collection

Nelson's Textbook of Pediatrics

Sweat Chloride Ranges

Diagnosis	Intermediate	Unlikely
• >60mmol/L	• 30-59mmol/L	• <30mmol/L
+ NBS Clinical history + Family history	Consider extended CFTR genetic analysis	CF is unlikely

Lebecque P et al. Mutations of the cystic fibrosis gene and intermediate sweat chloride levels in children. Am J Respir Crit Care Med. 2002;165: 757–61.

Guidelines (CF Foundation)

Diagnostic Definitions

CF

- clinical presentation and CFTR dysfunction

CFMS/CFSPID

- Infants with positive NBS AND EITHER:
  - Sweat chloride <30 + 2 CFTR mutations
  - Indeterminate sweat chloride and 1 or 0 mutations

CFTR-related

- Symptoms that related to CFTR dysfunction but not full CF criteria

Guidelines (CF Foundation)

Indeterminate Sweat – Thoughts?

- Sweat chloride = good discriminating test but **normal adults can have values as high as 50 and 60**
- Sweat chloride values increase with age → higher with normal adolescents and adults
- Does lowering the borderline cut-off for sweat chloride impact the diagnostic process?

1. *Hodson et al. (1983). Sweat test used to diagnose CF in adults, BMJ*

2. Leigh, M (2004). Diagnosis of CF despite normal or borderline sweat chloride. Paeds Resp Reviews

3. Ciriilli et al (2018) May the new suggested lower borderline limit of sweat chloride impact the diagnostic process for CF?" The journal of Pediatrics

Borderline sweat test: Utility and limits of genetic analysis for the diagnosis of cystic fibrosis☆

Manuela Seia [a,*], Lucy Costantino [a], Valentina Paracchini [a], Luigi Porcaro [a], Patrizia Capasso [a], Domenico Coviello [a], Carlo Corbetta [b], Erminio Torresani [c], Domenico Magazzù [d], Vincenza Consalvo [a], Alice Monti [e], Diana Costantini [e], Carla Colombo [e]

- CFTR mutation analysis and borderline sweat chloride concentration
- The mean value in the DNA negative subjects was significantly lower than in those with at least one CFTR mutation
- Subjects with a sweat value <39 mEq/l are ***unlikely to carry variant/mutation in the CFTR gene*** and genetic analysis may be performed only in subjects with chloride values >39 mEq/l.

Elevated Sweat Chloride Levels and Asthma

IS THERE AN ASSOCIATION?

Sweat Chloride Levels and Asthma

- Research suggests there could be a link between higher sweat chloride levels in asthmatics compared to healthy controls
  - Generally, these values are still under 40mmol/L
- Others have not found a difference between healthy controls and those with asthma
- A history of several asthma exacerbations and recurrent pneumonia should prompt consideration of a sweat test

Awasthi et al. Higher sweat chloride levels in patients with asthma: a case-control study. Indian J Pediatr. 2014.
Gharib et al. Sweat chloride concentration; a comparative study in children with bronchial asthma and with cystic fibrosis. Am J Dis Child. 1965;109:66–8
Mandal et Kabra, Sweat Chloride Levels in Asthma Indian J Pediatr (February 2015) 82(2):103–104

.

Sweat Chloride Levels and Asthma

- ?related to Ventolin use (selective beta-2 agonist)
  - Hypokalemia ⟶ increased chloride levels
- Asthmatics are more likely to receive steroids
  - associated with sodium retention which directly correlates with increased level of chloride in sweat.

Awasthi et al. Higher sweat chloride levels in patients with asthma: a case-control study. Indian J Pediatr. 2014.

Severe asthma and cystic fibrosis: Overlapping phenotypes?

Giovanna Riolo[a], Kelly M. Rodrigues[b,c], Cathy E. Dai[b,c], Andrew G. Day[d], and M. Diane Lougheed[b,c,d]

[a]Department of Medicine, St. Michael's Hospital, Toronto, Ontario, Canada; [b]Asthma Research Unit, Kingston Health Sciences Centre, Kingston, Ontario, Canada; [c]Department of Medicine, Queen's University, Kingston, Ontario, Canada; [d]Clinical Research Centre, Kingston General Hospital Research Institute, Kingston, Ontario, Canada

- ~10% of individuals with asthma have severe disease
- Heterozygosity for CF has been associated with increased airway reactivity → airflow obstruction
- Heterozygosity for CFTR gene mutations → ?predisposition to the development of asthma
- Possible association between CFTR mutations and asthma severity

Severe asthma and cystic fibrosis: Overlapping phenotypes?

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[a]Department of Medicine, St. Michael's Hospital, Toronto, Ontario, Canada; [b]Asthma Research Unit, Kingston Health Sciences Centre, Kingston, Ontario, Canada; [c]Department of Medicine, Queen's University, Kingston, Ontario, Canada; [d]Clinical Research Centre, Kingston General Hospital Research Institute, Kingston, Ontario, Canada

- Some studies suggest an association between being heterozygous for a CFTR gene mutation and forms of pulmonary diseases, including asthma and ABPA.
  - Others have suggested CFTR mutations may be protective against bronchial asthma (or no relationship at all)
- ATS/ERS and CTS recommend screening for CF in cases of severe asthma

Miller PW et al. Cystic fibrosis transmem- brane conductance regulator (CFTR) gene mutations in allergic bronchopulmonary aspergillosis. *Am J Hum Genet* 1996, 59:45-51.

Risk of asthma in heterozygous carriers for cystic fibrosis: A meta-analysis

Anne Orholm Nielsen[a], Sadaf Qayum[a], Pierre Nourdine Bouchelouche[a], Lars Christian Laursen[b], Ronald Dahl[c], Morten Dahl[a,*]

- The risk of asthma was significantly higher in people heterozygous for CF than in non-carriers
- Is asthma a CFTR-related disorder?
  - reduction of CFTR function vs interaction

Non-allergic asthma as a CFTR-related disorder☆

Angela Schulz, Burkhard Tümmler *

- CF-like symptoms with inconclusive CFTR genotype and sweat chloride concentrations → non-allergic asthma
- Childhood history of obstructive lung disease and recurrent airway infections.
- The sweat chloride: **normal to borderline range**
- A CFTR-related disorder may manifest in childhood with obstructive lung disease that is classified as an intrinsic or non-allergic asthma

Case: Additional Results

- common CF genetic mutations - **pending**
- cough swab: negative
- fecal elastase: **indeterminate range**
- liver enzymes, glucose and iron studies - normal
- repeat immunoglobulins and vaccine titres - normal
- nasal brush biopsy – **pending**
- Vitamin A level: **low**

Take Home Points

- If the "asthma" doesn't fit like asthma, trust your gut
- Consider the broad differential for asthma and if suspected, include additional investigations such as lung volumes, sweat test, bronch with BAL, HRCT, PCD
- Children with asthma have been found to have higher sweat chloride levels than their "non-asthma" peers, although this is still usually in the normal range
- Sweat chloride levels tend to increase with age, so normal adolescents and adults may have a sweat chloride over 50-60

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Questions?


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