34* A novel paradigm for attributing the diagnosis of CF disease

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Diagnosis of CF based on diagnostic algorithms is unsatisfactory due to inadequacy of genotyping and considerable overlap and poor concordance with sweat chloride (SC) and nasal potential difference (NPD). We evaluated a novel approach using principal components analysis (PCA) as a diagnostic determinant of CF. PCA is not dependent on assumptions of original test cutoffs and can integrate multiple variables (SC & NPD) while retaining information of the original variables.

Methods: Patients with suspected CF (Q), and reference non-CF (healthy individuals [CON] and obligate heterozygotes [HET]) and CF subjects (PS & PI) were evaluated by genotyping, SC & NPD. PCA was performed on various combinations of SC and NPD parameters. Based on PCA, the risk of CF diagnosis ranging from 0 to 100%, was determined by logistic regression.

Results: Optimal separation, with no overlap, was observed between CF and non-CF individuals with PCA of SC and 2 NPD parameters (ΔCl-free+Iso and ΔAmil+Cl-free+Iso) (Table). There was contiguity of dysfunction and probability of CF diagnosis from CON to HET at one extreme to CFPS and CFPI at the other. Similar contiguity was observed in Q patients, which correlated with the number (0, 1 or 2) and severity of CFTR mutations (CF- or not CF-causing).

Conclusion: An integrated ion channel measurement may offer optimal determination of the risk of a CF diagnosis, in patients with an uncertain diagnosis of CF.

Integrated ICM and probability of CF diagnosis

Group	N	PCA of integrated ion channel measurement: SC, ΔCl-free+Iso and ΔAmil+Cl-free+Iso; value (probability of CF, %)				
		Min	Lower quartile	Median	Upper quartile	Max
CON	84	−4.4 (0)	−2.1 (0)	−1.4 (0.1)	−1 (0.7)	−0.2 (29.3)
HET	48	−3 (0)	−1.7 (0)	−0.9 (1.0)	−0.6 (5.0)	−0.2 (27.3)
CFPS	64	0.2 (64.4)	0.9 (98.4)	1.5 (99.9)	2.1 (100)	3.4 (100)
CFPI	43	1.4 (99.9)	2.3 (100)	2.6 (100)	2.8 (100)	3.7 (100)

35 CF diagnosis algorithms: challenging dogma

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A diagnostic algorithm, incorporating CFTR genotyping, sweat chloride (SC) and other ion channel tests e.g. nasal potential difference (NPD), has been developed by ECFS to assist CF diagnosis (*Thorax* 2006;61;627−635). We used prospectively ascertained data to independently test the validity of the algorithm.

Methods: Patients with suspected CF (Q: idiopathic sinopulmonary disease, idiopathic pancreatitis, obstructive azoospermia) and reference groups of healthy individuals (CON), obligate heterozygotes (HET) and CF patients (PS and PI) were evaluated. No prior assumptions were made for the diagnostic reference range for NPD since none has been established or validated. Hence, reference ranges were based on the degree of overlap between CF and non-CF individuals.

Results: Variable overlap occurred in SC & NPD between CF and non-CF (Table). Observed agreement between SC & NPD was ⩾95% in CFPI and CON groups but suboptimal in CFPS and Q groups (confirmed on Kappa [κ] statistic; excellent agreement if κ > 0.8). Genotyping offered no additional diagnostic yield.

Conclusion: Diagnosis of CF, by genotyping and using SC & NPD separately and stepwise, is unsatisfactory; not only in uncertain cases but also in a small number of patients with clear-cut normal/abnormal results.

Outcomes and concordance of diagnostic evaluation.

Group	N	2 CF causing mutations: n (%)	SC (mmol/L): median, range	NPD ΔCl−free+iso (mV): median, range	eΔCl−free+Iso/Δamil: median, range	SC and ΔCl−free+iso	SC and eΔCl−free+Iso/Δamil
CON	84	0	18, 10−52	−23, −59 to −8	0.11, 0.00−0.61	95%; −0.02 (−0.05, 0.00)	100%; −
HET	48	0	24, 10−59	−19, −48 to −8	0.29, 0.02−0.57	69%; −0.15 (−0.26, −0.04)	100%; −
Idiopathic sinopulmonary disease	72	4 (6%)	25, 10−89	−13, −51 to 14	0.35, 0.00−6.05	77%; 0.58 (0.40, 0.76)	87%; 0.64 (0.43, 0.85)
Idiopathic pancreatitis	44	2 (5%)	24, 10−100	−15, −60 to 8	0.29, 0.00−1.85	64%; 0.10 (−0.13, 0.33)	76%; −0.08 (−0.17, 0.01)
Obstructive azoospermia	92	4 (4%)	44, 10−108	−9, −40 to −5	0.61, 0.03−1.28	44.6%; 0.24 (0.09, 0.40)	62%; 0.22 (0.05, 0.39)
CFPS	64	28 (44%)	67, 10−125	0, −12 to 14	1.00, 0.61−1.95	64%; 0.04 (−0.07, 0.15)	64%; 0.00 (0.00)
CFPI	43	38 (88%)	102, 68−121	3, −4 to 17	1.10, 0.85−3.21	100%; −	100%; −

36 CFTR-related disease: clinical characterization and long term follow up

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Background: The term CFTR-related disease describes individuals with CF phenotype or positive neonatal screening (NBS), normal or borderline sweat chloride test (SCT) and one disease-causing mutation on each CFTR gene.

Aim: To characterize the clinical features and the long-term follow-up of patients with CFTR-related disease followed at our Center.

Patients and Methods: We studied 68 subjects (41 females) responding to the definition of CFTR-related disease. Median age was 7.9 yrs (range 0.2−25 yrs), median follow-up time 5.6 yrs. CFTR mutation screening was performed with DGGE, DHPLC and sequencing. Pancreatic status was established by means of faecal elastase.

Results: Diagnosis occurred by means of NBS in 50 (73.5%) and by symptoms in 18 (26.5%). All 68 subjects are compound eterozygous carrying at least one mild mutation and all are pancreatic sufficient. At the first visit, 34 (68%) of infants diagnosed by NBS were asymptomatic. Children diagnosed by symptoms had mostly respiratory symptoms (12 pts, 68.8%) with lower RTI in 10. During the follow-up 22 children became symptomatic mainly with URTI; their SCT values were higher (44 vs 30 mEq/l Cl) than those found in patients who remained asymptomatic. Pts >10 yrs of age show more evident lung disease (50% Gram neg colonization).

Conclusions: Pts with CFTR-related disease are pancreatic sufficient and most have a borderline or negative SCT. They show no symptoms in early life and mild lung disease beyond the age of 10 yrs. NBS programs result in increasing detection of CFTR related-disease.

37* Jejunoileal atresia and cystic fibrosis: Don't miss it!

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Introduction: Three neonates with jejunal or ileal atresia (JIA) were diagnosed with CF in a year time, only after a considerable doctor's delay. In one of those cases the diagnosis was established post-mortem. A neonate presenting with meconium ileus will lead neonatologists and surgeons to perform CF analysis, but JIA may not.

Aims and Objectives: Analysis of all cases of JIA in a University Hospital with a Neonatal Intensive Care Unit (NICU) and a dedicated CF-team.

Methods: Retrospective chart review and comparison with current literature.

Results: In our hospital, in an 18 year period (1991−2008), 55 children presented with JIA. CF was only considered in 19/55 cases (35%), which led to 4 diagnosed cases (4/19, 21% of those considered) with a sweat test (n = 3) or CFTR analysis (n = 1). Of the four children with CF, one was diagnosed in the first month after birth, another at age four months, and the other two at age seven months (one was post-mortem).

In current international pediatric (including CF), surgical and genetic textbooks, as well as in the OMIM database, JIA is not mentioned as a possible presenting clinical feature of CF and therefore not listed as an indication to perform a sweat test or DNA analysis. In the few PubMed-cited articles reporting this association, the prevalence of CF in JIA patients is approximately 10% (range 8−11%).

Conclusion: In our hospital the, scarcely reported, association between JIA and CF was underappreciated until now. Physicians treating neonates with bowel obstruction must be aware of the reported prevalence of approximately 10% CF in JIA and act accordingly.

Jejunal or ileal atresia: consider CF!