

5th Annual Meeting of the ECFS - Diagnostic Network Working Group / EUROCARE CF WP3 diagnosis

Liverpool, United Kingdom, February 19th to 21st

February 19th was organised in collaboration with PTC Therapeutics as a satellite session on standardisation of nasal potential difference (NPD) for the upcoming PTC Trial.

The meeting started with Steven Rowe from Birmingham, Alabama who gave an update on the PTC NPD standardisation process. Thereafter, we continued with a practical NPD training session to show NPD measurements to centres who will be starting NPD for this trial and exchange experiences between the centres already performing NPD.

February 20th.

Scientific presentations:

1. Francois Vermeulen started the meeting by showing his NPD comparative studies: in one nostril he used the "Knowles method" to measure NPD, placing the catheter under the inferior turbinate, using the perfusion method and calomel electrodes with a subcutaneous needle as reference bridge. In the other nostril he used the Foley catheter, non-perfusion, with the hole at the side and measuring on the nasal floor, the "Alton method". He saw no differences in mean values and SDs between both methods. In addition, he gave an overview of reference values published before which also shows similar results for floor and turbinate measurements.
2. Inez Bronsveld showed the update on the evaluation and standardisation process for NPD in Europe. All participating NPD centres can distinguish between CF and non-CF, however there can be differences between values from different centres. Because of the variation in NPD protocols between centres we cannot identify at present, which factors cause the differences in results. These results show the necessity for a standard operating procedure for the different NPD centres.
3. Peter Middleton presented the difference in NPD by using a low chloride solution versus a Cl-free solution. The Cl-free solution gave a bigger response (2 mV) in NPD in control persons. In CF there was no difference between 0 or 6 mM chloride concentration. He also showed PD values measured with solutions with or without glucose 20 mM without any effect.
4. Maarten Sinaasappel showed us the development of a new protocol for intestinal current measurement (ICM) by using a wash out period after the Carbachol addition followed by the addition of Forskolin, Genistein, and finishing with another Carbachol addition. When you add the Forskolin + Genistein + Carbachol responses you get a much larger response in the control patients.
5. Nico Derichs from Hannover, Germany has been collecting ICM data from European CF centres on their methods used. He showed that practically 2 diverse methods are presently being used: the Rotterdam method which is non-perfusion and the Freiburg method which is a continuous perfusion method. The former method is a short-circuit measurement (Isc), while the latter measures the trans-epithelial voltage (Vte). This method showed a little less drift, however it is difficult to detect residual secretion in this method.
6. Halyna Makukh showed the CF diagnostic challenges in the Ukraine and the genetic analysis where 17 different mutations were found, including the 2184insA mutation and aims to include this mutation in the diagnostic panel for a better diagnostic process in the Ukraine.
7. Our host Kevin Southern presented us the pitfalls for the sweat test (ST). He advised to keep performing ST for babies, because a negative newborn screening test (NBS) does not exclude CF.

In the NBS group in Australia with negative immuno-reactive trypsinogen (IRT) are now some patients coming back with symptoms and appearing to have CF. The experience is that the used NBS test misses about 10% of the CF patients.

8. Nick Simmonds presented the nasal airway ion transport and relationship with long term survival in CF (Resp Med, 2009). He showed that ST and NPD do not correlate with FEV1 and FVC. However, BMI has one of the strongest correlations with long term survival in patients over 40 years of age.
9. Harry Cuppens gave us an update on the R117H mutation. R117H-5T is only found in CF patients. R117H-7T can be identified in CBAVD but also in CF patient with mild disease or no disease at all. When you find a R117H mutation, the status of the Tn polymorphism in IVS8 should always be established. Dr Cuppens also mentioned the CFTR-2 project. This initiative aims to produce a database with CFTR mutations, functional studies and clinical data.
10. Martin Schwarz reported on difficult CFTR mutations, also called intermediate variations in the cftr gene. They fall into 2 classes: the ones seen before with known clinical associations, of the others you need to collect empirical evidence; and the ones not seen before for which it is difficult to predict disease association and severity. There is a new development of computer programs that predict if mutations are tolerated and will not have consequences or whether a mutation will show clinical phenotype.
11. Kris De Boeck discussed the new "North American consensus" published in the Journal of Pediatrics (2008). Discussion points were if it is necessary to use the same pathway for NBS and for patients with a history of symptoms, why NPD is degraded to an ancillary test and why we do expensive CFTR sequencing if only 23 mutations are acknowledged as CF causing.
12. On the 21st of February David Sheppard gave a thorough overview of different patch-clamp methods and the possibilities with the different cell configurations in this technique, like inside-out and outside-out. He also showed some nice slides of the newer set-ups for patch-clamping that, with the new available equipment, are much smaller than the former set-ups.
13. Andrea van Barneveld reported on CFTR expression. From the European Twin and Sibling Study we know that there are F508del homozygous patients with residual chloride secretion. She investigated 12 CF patients of which 10 showed residual secretion, but up till now she found no correlation between the CFTR protein expression bands and residual secretion in the ICM measurements.
14. Jim Wild presented studies on MR imaging for CF lung disease and showed comparisons between CT scan images and MR imaging to determine lung disease.
15. Erol Guillard performed NPD in babies and showed that the maximal PD increases from 23 weeks to 36 weeks and then levels off. He emphasised on the differences in procedures between babies and adults.
16. Jane Davies discussed the gene therapy trial that has just started in London with the first included patient and showed us impressive slides on lower airway ion transport to judge effectiveness.

Our next meeting will be in Brest at the ECFS conference on June 10th 2009. The Annual Meeting of the ECFS-DN WG for next year will be held in Paris, France.

Reporters: Inez Bronsveld and Michael Wilschanski