22nd Scientific Meeting

Diagnosis and Diagnostics in CF - From newborn screening to advanced disease in the age of CFTR modulators

28th – 29th September 2023

Schloss Montabaur (Germany)

MUKOVISZIDOSE
Mukoviszidose Institut gGmbH

Organization

Scientific advisory board of the German Research Community for Cystic Fibrosis (FGM) & Mukoviszidose Institute gGmbH (MI)

Chairs

Jutta Hammermann (DE/Dresden)
Mark Oliver Wielpütz (DE/Heidelberg)

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Please not that not all talks have a published abstract.

Program

Thursday, September 28th

1:00-1:15 pm — **Opening of the meeting**

Chairs of the meeting
Jutta Hammermann (DE/Dresden)/Mark Oliver Wielpütz (DE/Heidelberg)

Chair of the German CF Research Community (FGM)
Mirjam Stahl (DE/Berlin)

1:15-2:15 pm — **Session I: Structural Imaging with CT**
Moderators: Jim Wild (UK/Sheffield) / Mark Oliver Wielpütz (DE/Heidelberg)

1:15-1:45 pm — **Young lung: Novel CT-Techniques, Fast, Low and Ultra-low Dose**
Daan Caudri (NL/Rotterdam)

1:45-2:15 pm — **Young to Old: Automated CT Quantification – Influence of Dose and Results from Clinical Trials**
Oliver Weinheimer (DE/Heidelberg)

2:15-2:45 pm — *Break*

2:45-4:15 pm — **Session II: Functional Imaging with MRI**
Moderators: Daan Caudri (NL/Rotterdam) / Mark Oliver Wielpütz (DE/Heidelberg)

2:45-3:15 pm — **Ventilation MRI with Hyperpolarized Gases – Novel Insights Into CFTR-Modulator Therapy**
Jim Wild (UK/Sheffield)

3:15-3:45 pm — **Early to End Stage Lung: Bronchial Artery Hypertrophy – Diagnosis and Implications for Patient Care**
Mark Oliver Wielpütz (DE/Heidelberg)

3:45-4:15 pm — *Break*

4:15-5:15 pm — **Session III: Extrapulmonary Manifestations**
Moderators: Katja Glutig (Berlin/DE) / Mark Oliver Wielpütz (DE/Heidelberg)

4:15-4:45 pm — **Imaging of the Paranasal Sinuses – Implications of Modulator Therapy**
Lena Wucherpfennig (DE/Heidelberg)

4:45-5:15 pm — **Imaging Abdominal Manifestations in CF – Changing Paradigms in the Modulator Era**
Katja Glutig (Berlin/DE)

5:15-5:30 pm — *Break*

5:30-6:20 pm — **Keynote-Session**
Moderators: Jutta Hammermann (DE/Dresden) / Mark Oliver Wielpütz (DE/Heidelberg)

Young Lung: Non-Contrast Ventilation and Perfusion Imaging with 1H-MRI – Correlation with Clinical Metrics
Grzegorz Bauman (CH/Basel)

Friday, September 29th

8:30-8:45 am	**Opening second day**
8:45-10:15 am	**Session IV: Newborn Screening** *Moderators: Anne Munck (FR/Paris) / Jutta Hammermann (DE/Dresden)*
8:45-9:15 am	**Updated guidance on the management of children with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID)** Jürg Barben (CH/St. Gallen)
9:15-9:45 am	**CF-NBS in Europe - European survey of newborn bloodspot screening for CF: opportunity to address challenges and improve performance** Anne Munck (FR/Paris)
9:45-10:15 am	**5 years of CF newborn screening in Germany – Experience and ideas for optimizing the algorithms** Ute Holtkamp (DE/Hannover)
10:15-10:45 am	*Break*
10:45-11:30 am	**Abstract-Session** *Moderators: Jutta Hammermann (DE/Dresden) / Mark Oliver Wielpütz (DE/Heidelberg)*
10:45-11:00 am	**Proof of concept of ionocytes' CFTR content as a novel biomarker for cystic fibrosis diagnosis and follow up** Floriana Guida (Genoa/IT)
11:00-11:15 am	**The changing landscape of reproductive counselling in people with cystic fibrosis: Insights from patients and care teams** Stefan Reinsch (Neuruppin/DE)
11:15-12:00 pm	*Break*
12:00-1:00 pm	**Session IV: Validation of diagnosis and therapeutic benefits** *Moderators: Simon Gräber (DE/Berlin)/ Jutta Hammermann (DE/Dresden)*
12:00-12:30 pm	**Improvements in Sweat Testing for Diagnosis and Follow-Up: the ß-adrenergic Sweat Secretion Test** Sophia Pallenberg (DE/Hannover)
12:30-1:00 pm	**nPD vs. ICM vs. Organoids– Value in First Diagnosis and Therapeutic Intervention** Simon Gräber (DE/Berlin)
1:00 pm	**Closing of the Meeting**

Session I: Structural Imaging with CT

Young to Old: Automated CT Quantification – Influence of Dose and Results from Clinical Trials

Oliver Weinheimer

Chest computed tomography (CT) remains the imaging standard for demonstrating cystic fibrosis (CF) lung disease in vivo. Optimal characterisation of early structural abnormalities has been highlighted as critical to future efforts to detect and prevent CF lung disease progression. Visual scoring systems are time consuming, require training and lack high reproducibility. Quantitative computed tomography (QCT) techniques deliver useful and objective biomarkers describing the lung parenchyma and the airways. QCT parameters can provide information about the progression of the disease, about the response to therapy, and can also help to identify regional and temporal interdependencies of distinct manifestations of CF lung disease. However, QCT in CF is challenging because most available techniques were primarily developed for adults and cannot be applied directly to CT scans of children with CF. Another challenge is the dose – low dose (LD) CT is almost established as a standard in lung CT imaging. A recent publication highlights the potential utility of ultra-low dose (ULD) CT to reduce radiation burden in this susceptible population.

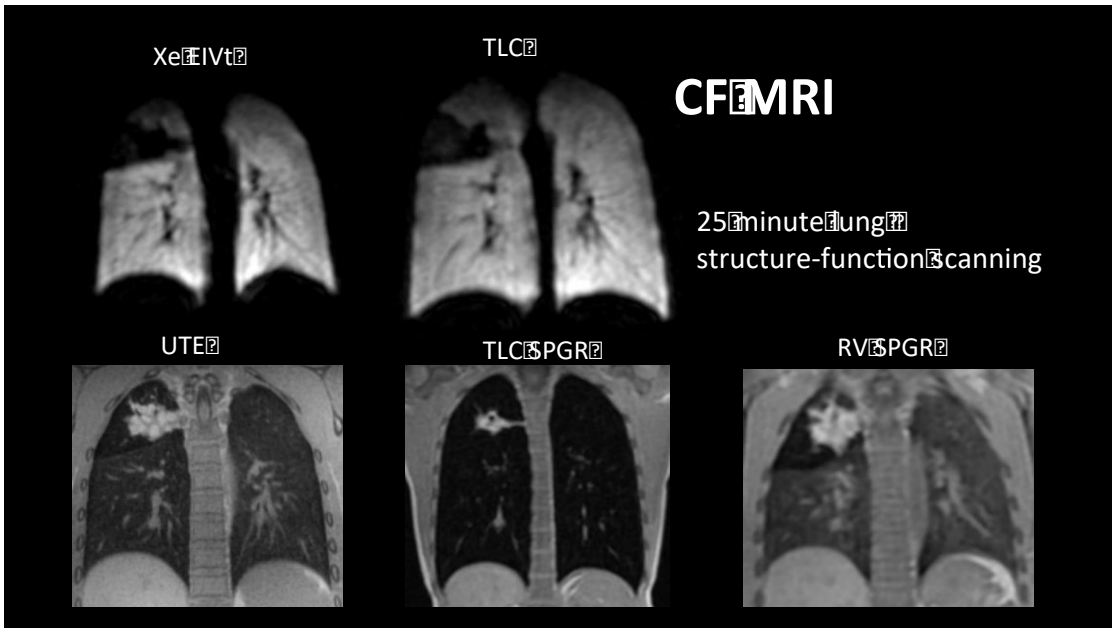
Session II: Functional Imaging with MRI

Functional and structural lung MRI to detect early abnormalities and change in cystic fibrosis

Jim Wild

MRI offers distinct advantages over CT for early disease detection in CF, being radiation free and capable of measuring both function and structure. Hyperpolarised gas ventilation MRI is highly sensitive to early lung disease and 1H MRI sequences can be used to generate high-resolution images for detection of structural disease.

This invited talk will highlight the ability of different MRI sequences to detect CF-related lung abnormalities draw on work from the group in Sheffield with 3He, 129Xe and 1H lung MRI studies in children and adults with cystic fibrosis.



Early to end-stage Lung: Bronchial Artery Hypertrophy – Diagnosis and Implications for Patient Care

Mark O. Wielpütz

After more than 15 years of continued efforts, chest MRI has emerged as an imaging modality sensitive to detect morphological and functional abnormalities in the lungs of cystic fibrosis (CF) patients, as well as response to therapy with antibiotics and CFTR modulators, in all age groups. Specifically, perfusion MRI has proven to be an important marker of small airway obstruction in CF. Lung perfusion is regulated on the level of the pulmonary lobule, which is the smallest functional unit of the lung periphery, by so-called hypoxic pulmonary vasoconstriction (HPV, also known as 'Euler-Liljestrand-Reflex'), which couples lung perfusion to lung ventilation. In obstructive airway diseases such as CF reversible obstruction or obliteration of the small peripheral airways leads to downregulation of pulmonary perfusion in order to reduce intrapulmonary shunts and to distribute blood flow to functional lung areas in order to conserve optimal oxygenation for the systemic circulation. Interestingly, lung perfusion abnormalities improved after therapy with antibiotics in preschool and school-age children, but did not change in adolescents and adults under therapy with triple combination CFTR modulators. As a second system of nutritive blood supply for the lungs themselves, the bronchial arteries arising from the aorta carry oxygenated blood to the lungs and bronchi ('vasa privata'), accounting for less than 1% of the left cardiac output directed to pulmonary blood inflow in healthy individuals. In CF hypertrophy may occur due to chronic regional hypoxia and inflammation, and lead to an increased inflow from the systemic circulation in advanced CF lung disease. My presentation aims as identifying conditions with bronchial artery dilatation (BAD) in CF patients and its clinical implications. BAD may indicate irreversible changes in lung perfusion in CF patients, but which has not been investigated to date. Thus, most recent evidence on changes of BAD under therapy with CFTR modulators will be discussed.

Session III: Extrapulmonary Manifestations

Imaging of the Paranasal Sinuses – Implications of Modulator Therapy

Lena Wucherpfennig

In patients with cystic fibrosis (CF) chronic rhinosinusitis (CRS) is often underrecognized due to the early predominance of pulmonary symptoms, but significantly contributes to morbidity. Moreover, CRS may serve as a reservoir for bacteria and leading to recurrent infections of the lower airways. Computed tomography (CT) studies reported that sinonasal opacification was present from shortly after birth and that the degree of opacification was associated with a severe course of CF, suggesting thorough examination of the paranasal sinuses in children with CF. Due to the accumulating radiation dose especially in infants and preschool children the use of CT is limited for short-term follow-up and lifelong monitoring of paranasal sinus abnormalities. Moreover, the limited tissue contrast of CT may be insufficient to distinguish early and distinct structural sinus abnormalities in CF. Recently, magnetic resonance imaging (MRI) was introduced as a sensitive, non-invasive, and radiation-free diagnostic tool for the detection and monitoring paranasal sinus abnormalities in CF and a dedicated CRS-MRI scoring system was developed.

This presentation will demonstrate the ability of paranasal sinus MRI in combination with a dedicated CRS-MRI scoring system for the longitudinal assessment of CRS severity and will highlight improvements in CRS severity under cystic fibrosis transmembrane conductance regulator (CFTR) modulators in patients with CF.

Imaging Abdominal Manifestations in CF - Changing Paradigms in the Modulator Era

Katja Glutig

The presentation will focus on advances in imaging in CF patients: New imaging modalities and innovative technologies that may improve diagnosis and monitoring of abdominal manifestations in CF, especially under modulator therapy. Cystic fibrosis is coming of age. Thanks to continuously improved symptom-based therapies and the use of modulators, CF patients are currently predicted to live beyond 50 years. The focus is increasingly shifting towards the non-pulmonary manifestations of CF. Abdominal complications may be attributed to loss or altered function of CFTR in the pancreas, intestine, and hepatobiliary system. It is critical to assess liver disease appropriately. To date, ultrasound has been used to detect liver involvement in the presence of hepatomegaly or splenomegaly, portal hypertension, bile duct dilations, and microgall bladder. Innovative examination methods using multiparametric ultrasound have been helpful in diagnosing focal biliary or multilobular cirrhosis. Measurement of liver stiffness using shear wave elastography can predict the severity of liver changes and effectively monitor them under treatment with highly effective modulators. Liver stiffness is a quantitative and accurate marker. In certain cases with normal ultrasound, MRI with elastography and mapping for fat fractionation may be beneficial. Quantitative MRI results correlate with multiparametric ultrasound. Innovative imaging techniques can also monitor the effects of modulator therapy in exocrine pancreatic insufficiency. Ultrasound-based measurement of pancreatic elasticity can help detect pancreatic insufficiency at an early stage and contribute to positive long-term outcomes. Impaired bowel function can contribute to the development of liver fibrosis and bowel lesions. Here, MRI with innovative and rapid sequences can provide insight into the pathophysiology of CF and gastrointestinal obstruction without harmful radiation exposure. Subclinical ileal obstruction may be more common than previously thought. Gastrointestinal MRI with fast AI-guided sequences that can be acquired during free breathing is proving to be a promising diagnostic tool. Modulator therapy has beneficial effects on abdominal involvement in cystic fibrosis, and innovative ultrasound and magnetic resonance imaging with AI support are useful to assess changes noninvasively.

Keynote Session

Non-contrast functional imaging of cystic fibrosis lung disease

Grzegorz Baumann

Lung function tests are the most commonly used diagnostic tool to assess lung function. While inexpensive and practical, they cannot locale the exact origin of functional impairment or depict single-sided functional changes. Hence, numerous diseases with impairment of lung function, as well as monitoring of therapeutic response, call for dedicated imaging technology. Over the past years, substantial progress has been achieved in the development of non-invasive and free of ionizing radiation magnetic resonance imaging (MRI) methods for the evaluation of lung function. These techniques are largely based on the extraction, separation, and analysis of signal modulations in the lung parenchyma caused by respiration and blood flow. One of the techniques which was more widely explored is matrix pencil decomposition MRI (MP MRI). The technique allows for a simultaneous assessment of lung ventilation and perfusion from a single time-resolved free-breathing acquisition. As a fully non-invasive technique, MP MRI is especially well-suited for application in pediatric patients. In the past years, the technique has been validated in numerous studies with other gold-standard imaging techniques, as well as compared to pulmonary function tests and nitrogen multiple breath-washout technique. MP MRI has demonstrated its utility as a tool for short and long-term monitoring of cystic fibrosis disease or monitoring of therapeutic response. Future studies with MP MRI may focus on further cross-validation with established diagnostic techniques in larger patient cohorts, multi-center studies, and standardization of the outcome parameters describing the functional lung impairment.

Session IV: Newborn Screening

CF-Newborn Screening in Europe - European survey of newborn bloodspot screening for CF: opportunity to address challenges and improve performance.

Anne Munck (on behalf of the ECFS Neonatal Screening Working Group)

The aim of this study was to record the current status of newborn bloodspot screening (NBS) for CF across Europe and assess performance. Methods We conducted a cross-sectional survey. We recorded national and regional programmes in Europe in 2022. We obtained protocol detail through a questionnaire and analysed outcome data for 2019, in order to compare the performance of different approaches to screening. Performance was assessed through a framework developed in a previous exercise. Programmes were classified as national or regional. Results: In 2022, we identified 22 national and 34 regional programmes in Europe. Barriers to establishing NBS included cost and political inertia. Performance was reported by 21 national and 21 regional programmes. All programmes employed different protocols, with IRT-DNA being the most common strategy. Six national and 11 regional programmes did not use DNA analysis. This survey demonstrates some areas of good practice in agreement with the ECFS standards of Care but there is considerable scope for improvement in the quality of NBS for CF across Europe. Integrating DNA analysis into the NBS protocol improves PPV, but at the expense of increased carrier and CFSPID recognition which is a concern and should be monitored. There is a drive for more extensive gene analysis and our survey shows that this can be incorporated into a programme in a manner to improve performance whilst minimizing negative impacts. Another limitation concerns the sensitivity as there is still no standardized recording of CF cases missed by NBS and we know little about their age range at diagnosis, symptoms, demographics, stage of the NBS programme when this can happen (false negative cases NBS protocol related (analytical issue) or non-protocol related (pre-post analytical issue). Conclusion: The framework of the twenty parameters to calculate the eight key outcomes established by the NSWG should be part of any annual report of a CF NBS programme. This can improve future international surveys and enable more valid comparison of protocol performance with quality improvement plan, but this depends on continued high-quality data collection preferably through a central coordinated system.

5 years of CF newborn screening in Germany – Experience and ideas for optimizing the algorithms

Ute Holtkamp

Since September 2016, newborns in Germany are screened for Cystic Fibrosis (CF). Immunoreactive Trypsinogen (IRT) and Pancreatitis associated Protein (PAP) are used as biochemical markers in a three-stage process. Samples with an IRT result above the 99.9. percentile are reported as “screening positive” without any further tests (“failsafe” strategy). Samples with an elevated IRT concentration between the 99. and 99.9. percentile and an additional positive PAP result are analysed by PCR for the 31 most common mutations in the CFTR gene. According to the children’s guideline published in 2016, this screening algorithm was intended to be evaluated after 3 years, but this evaluation has not been performed yet.

Here, we present CF screening data from 777668 newborn dried blood samples, generated from March 2017 to June 2021 in Screening-Labor Hannover. In total, 783 cases were reported “screening positive” (0.10 %) and 140 of these were confirmed as CF later (17.9 %). 662 samples were found “screening positive” via “failsafe” strategy, of which 116 cases of CF were confirmed (17.5 %). Furthermore, 6191 newborns were tested positive for elevated IRT results between the 99. and 99.9. percentile. The following PAP analysis was positive in 23.2 % of those samples. The subsequent mutation analysis identified 18 of these 1437 newborns as either homozygous or compound heterozygous. All of those were confirmed as CF cases later (100.0 %). Additionally, 103 heterozygous newborns were reported as “screening positive”. In this cohort, only 6 cases of CF were confirmed (5.8 %).

The aim of the CF screening is to identify as many newborns affected by CF as possible while minimising false positive results. However, the current algorithm results in a large number of false positive cases. In earlier and more recent publications, various approaches have already been described achieving better results with the same analytical tools. Our data point out that there is the potential to significantly improve the CF screening process, especially in the “failsafe” cohort.

Abstract-Session

Proof of concept of ionocytes' CFTR content as a novel biomarker for cystic fibrosis diagnosis and follow up

Floriana Guida, Fabiana Ciciriello, Giulia Gorrieri, Ilaria Musante, Federico Alghisi, Maria Laura Panatta, Giulia Marini, Alessandro Fiocchi, Paolo Scudieri

Despite the huge progresses made in cystic fibrosis (CF) knowledge and care, the exact relationships between primary defects and different manifestations of the disease are still poorly understood. Newborn bloodspot screening (NBS) is an effective strategy for the early recognition of infants with CF. However, increasing number of infants with a positive NBS result have an inconclusive diagnosis (CRMS/CFSPID). Nevertheless, CF still is a diagnostic and therapeutic challenge in the case of rare variants that are associated with varying symptoms and are unlikely to enter clinical trials. Therefore, it is important to identify precise and disease-relevant biomarkers allowing a better understanding of CFTR mutations effects in vivo, and also useful as outcome parameters to accurately quantify the rescue of CFTR by novel modulators. In this context, the recent identification of the CFTR-rich airways ionocytes could highlight novel possibilities to monitor CFTR in CF patients' airways. Despite their low quantity, ionocytes express the highest levels of CFTR per cell and are relatively abundant in the upper airways. These findings suggest that quantitative analysis of CFTR could be efficiently done in these cells. The ionocytes can be collected by the minimal invasive nasal brushing procedure. Ionocytes' CFTR content was evaluated by immunofluorescence detection of CFTR and FOXI1 (as a ionocytes marker) combined with confocal imaging and analysis of the intensity of the CFTR signal in the apical membrane relative to that in the intracellular compartments. As a proof of concept, we investigated the genotype-phenotype-ionocytes' CFTR content relationships in a small cohort of non-CF, CF (with minimal and residual function mutations), and CRMS/CFSPID subjects. Moreover, we collected nasal cells from CF patients treated with LUMA/IVA and ELX/TEZ/IVA (pre, 30 days and 12 months post-treatment). In accordance with genotype-phenotype, we found increasing levels of ionocytes' CFTR content in the following groups: CF patients with severe mutations < CF patients with mild mutation/CRMS/CFSPID < CF patients treated with LUMA/IVA < CF patients treated with ELX/TEZ/IVA < non-CF individuals. This finding suggests that this type of analysis could be useful to investigate genotype–phenotype correlation and, possibly, the efficacy of CFTR pharmacotherapies. In addition, analyzing CFTR activity in airways ionocytes will be an important future step to better clarify their role in airways epithelium.

The changing landscape of reproductive counselling in people with cystic fibrosis: Insights from patients and care teams

Stefan Reinsch, Anne Klotsche

In recent decades, the improved general health of people with CF (pwCF) has led to a demographic change. Today, more than half of the German CF population are adults, many of whom are studying and working. In addition, and strongly influenced by modulator therapy, female fertility has increased. As a result, it has become a realistic possibility for women with CF to become pregnant and to care for and financially support children. At the same time, new technologies have become available for genetic testing for CF before, during and after pregnancy. This brings additional challenges to perinatal decision making, namely whether and when to know the genetic CF status of a potential child. We explore the changing landscape of reproductive care and perinatal counselling in cystic fibrosis through a qualitative interview study with people with cystic fibrosis and their care teams. We carried out 20 semi-structured interviews. We asked our interviewees about their experiences and attitudes, the medical and social circumstances in which pwCF now imagine having their own children, how they deal with medical, social and ethical challenges, and their counselling needs. The interviews were audio-taped, transcribed verbatim and analysed using a grounded theory approach. Members of the care team observe structural deficits and a changing need for perinatal counselling. Despite improved health, the unique challenges of CF mean that women with CF cannot imagine raising a child alone. Reproductive decisions are delayed to avoid single parenthood. However, after birth, conflicts and separations arise as the increased needs of pwCF that were covered by good health before pregnancy resurface. Prospective parents are aware that a child means less time for their own therapy. In order to avoid the situation of caring for a child, which is already considered challenging, plus a 'double therapeutic burden' of caring for the child's CF on top of their own CF, pwCF want to rule out having a child with CF. All pwCF interviewed agree that "earlier testing is better", which means that if pregnancy is planned, they would opt for carrier screening of the partner. At the same time, members of the care teams interviewed report that they are faced with an unexpectedly high rate of spontaneous and unplanned pregnancies in pwCF with different health conditions. For many people with cystic fibrosis, having a family is part of living a life worth living. Despite continuing deficits in the counselling infrastructure, all involved need to be aware that people with CF accept health risks for the sake of having children. Single motherhood by choice is not discussed as an option, but may occur when parents separate, requiring additional counselling and support. Carrier testing of the partner for CF is the preferred option to exclude the birth of a child with CF. The rationale is not to prevent a life with CF, but to avoid the double therapeutic burden of parent and child, and to protect the child from early infection with CF-specific pathogens via the caregiver.

An algorithm to identify sources of poor response to ETI: design of the tool and first experience *(only poster presentation)*

Federico Cresta, Nicoletta Pedemonte, Emanuela Pesce, Valeria Capurro, Alessia Cafaro, Giuliana Cangemi, Rosaria Casciaro, Francesca Mattioli, Carlo Castellani

Elexacaftor / tezacaftor / ivacaftor (ETI) is widely considered a life changer in pwCF (Cystic Fibrosis patients) carrying at least one F508del mutation. In the last few years, sporadic reports about lack of functional and clinical benefits, especially in terms of sweat chloride decrease, have emerged. Defining and detecting poor responders is challenging, because of the absence of standard criteria for treatment failure and the large variability of the response to ETI. The possible causes of a non-satisfactory response to ETI could be divided into reversible (poor adherence, pharmacological interactions) and non-reversible causes (CFTR complex alleles). We designed a diagnostic algorithm finalized to the detection and characterization of poor responders to ETI treatment. A sequence of consecutive steps begins with identifying the poor responding patient through a cumulative assessment of clinical evidence (PFT, number of PEx, BMI changes, CFQ-R) extended through a period of at least 6 months. This is followed by a cascade of further assessments, which can be interrupted at any stage if a basis for the lack of response is identified. This path moves from sweat test and proceeds through adherence and antagonists check, search of complex alleles, TDM, CFTR function assessment and CFTR sequencing. Analyses were performed as described below: 1. TDM technique For the quantification of ETI from plasma of pwCF, we developed and validated a liquid chromatography-tandem mass spectrometry (LC-MS/MS)method, validated following international (EMA) guidelines on validation of bioanalytical methods. 2. Primary Nasal cells cultures Nasal epithelial cells are obtained through nasal brushing of both nostrils. Airway epithelial cells are cultured in a serum-free medium in the presence of Rock and SMAD inhibitors to facilitate cell expansion. To obtain differentiated epithelia, nasal cells are seeded on porous membranes and kept under air-liquid interface (ALI) condition for 16-18 days. Transepithelial ion transport was then evaluated by short-circuit current recording in a Ussing chamber. Changes in CFTR-mediated current were measured upon sequential addition of amiloride, cAMP agonists, VX-770, and the CFTR inhibitor-172. 3. Genomic Analysis Peripheral blood samples are collected upon informed consent administration. Genomic DNA is extracted by a standard, automated procedure. Genomic DNA fragments corresponding to CFTR exons are amplified by PCR with specific primers, directly sequenced in both strands using a Big-Dye-Terminator v1.1 Cycle Sequencing kit. The algorithm was applied to screen 4 cases of possible poor responders, characterised by no response to ETI treatment in terms of Sweat Chloride, FEV1 and QoL. Primary nasal cell cultures confirmed severely reduced CFTR function and lack of response to ETI treatment in 3/4 cases. In these 3 pwCF molecular characterization highlighted the presence of an additional amino acid substitution, L467F, in cis with the F508del variant, demonstrating that these subjects were carriers of a complex allele. It is crucial to better understand and quantify the clinical and functional response to CFTR modulators, in order to identify poor responders. Equally important it is finding the mechanism of the lack of response, consequently making adjustments or stopping the drug, also in consideration of the limited knowledge on long term

side effects. In our hands this algorithm has proven useful, and needs validation with larger numbers. Some of the techniques used are not available in all CF Centres and require highly experienced staff, but, contrary to other tests like NPD or ICM, samples obtained locally can be couriered.

Acinetobacter baumannii infection in a child with Cystic Fibrosis: clinical description *(only poster presentation)*

Satenik Harutyunyan, Armine Terteryan, Karine Simonyan

Chronic infection of the airways remains the leading cause of morbidity and mortality in Cystic Fibrosis (CF) with Staphylococcus aureus and Pseudomonas aeruginosa as predominant pathogens. Over the last decades, there is an expansion of the spectrum of CF pathogens, and changes in the epidemiology of respiratory tract infection. Other pathogens that become prevalent are Stenotrophomonas maltofilia, Achromobacter xyloxidans, Burkholderia cepacia complex, non-tuberculous mycobacteria, Acinetobacter spp., and fungi. Although most pathogens from CF airways have been associated with poor outcomes and deterioration of lung function, the role of others remains uncertain, particularly Acinetobacter spp. In recent years Acinetobacter infection has influenced the epidemiology of nosocomial infection globally, becoming emerging with substantial multidrug- resistance. Limited data are present on clinical manifestations and disease course in CF patients infected with Acinetobcater spp.

We describe a case of a CF child with Acinetobacter baumannii in sputum with stable clinical deterioration, a gradual decrease in lung function, and FEV1. The patient carrying G542X/ 2183AA->G disease-causing mutations had poor weight gain, poor appetite, and school performance, fatigue, increased, foul smelling, grey sputum, and disturbing pertussis-like cough. Oxygen saturation was 93-94%. The patient was chronically infected with pseudomonas aeruginosa and was on long term inhaled colistin/tobramycin alternative regimen, with intravenous long courses of meropenem and amikacin, ceftazidim/amikacin during pulmonary exacerbations. Current sputum was negative for Pseudomonas, MSSA, MRSA, and Acinetobacter baumannii was detected. Oral minocycline 200mg/day for 21 days was added to the treatment with inhaled colistine, long-term azithromycin. Hyperbaric oxygenation was initiated. On the treatment fatigue and foul-smelling sputum disappeared, patient showed weight gain, a decrease in cough, an increase in oxygen saturation, and improvement in appetite and general condition. In Cystic Fibrosis Patients Acinetobacter baumannii should be considered as a disease-changing pathogen especially when colonization is accompanied by clinical signs such as poor weight gain or/and weight loss, decrease in FEV1, troublesome cough with foulsmelling sputum.

Session IV: Validation of diagnosis and therapeutic benefits

Improvements in Sweat Testing for Diagnosis and Follow-Up: the ß-adrenergic Sweat Secretion Test

Sophia Pallenberg

Cystic fibrosis (CF) is caused by a dysfunctional CF transmembrane conductance regulatory protein (CFTR) and includes numerous gradations beyond classic CF. Diagnosis can be challenging since sweat chloride concentrations may be in the intermediate range and advanced electrophysiological measurements using intestinal current measurement (ICM) and nasal potential difference (nPD) measurements are limited to a few centers and are restricted in their ability to differentiate between normal and high residual CFTR function.

The measurement of CFTR-dependent sweat secretion after β-adrenergic stimulation of the sweat gland, which was discovered in the 1980s, has not been established in routine clinical practice over the years due to difficulties in data collection, analysis, and standardization. With a novel experimental setup, automated recording and analysis of sweat bubble kinetics, we have simplified the performance of the β-adrenergic sweat secretion test (SST).

Previously, we demonstrated that measurement of CFTR-mediated β-adrenergic sweat secretion is a promising biomarker with a linear gradient of CFTR dysfunction in PI-CF, healthy heterozygous carriers, and healthy controls, with increased sensitivity in areas of high residual CFTR function. We have shown that β-adrenergic sweat secretion is suitable for therapy monitoring with CFTR modulators, while imposing more stringent requirements for wild-type CFTR conformation compared to other CFTR biomarkers. In addition, we have integrated SST in combination with sweat test, ICM, NPD and clinical findings in the assessment of individuals with suspected CFTR dysfunction. The presentation will address the advances and difficulties of this test compared to pilocarpine iontophoresis in diagnosing cystic fibrosis and monitoring CFTR modulator therapy for scientific questions, but also the importance for routine diagnostics in CF centers.

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