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Does C6-Ceramide induce activation of a rectifying chloride channel (ORCC) in vivo in patients with Cystic Fibrosis

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The hallmark of CF is a defective activation of chloride channels caused by mutations in the CFTR gene. Alternative pathways of chloride transport, independent of CFTR, represent a therapeutic concept for CF. It was shown that CD95 receptor triggering activates in peripheral blood lymphocytes from both healthy individuals and CF patients ORCC, an effect mediated by C6 ceramide and src-like tyrosine kinase p56lck. In this study we investigated the in vivo effect of ceramide on human respiratory epithelium using nasal potential difference measurement (nPD).

Methods: NPD was determined by measuring the potential difference in values between an exploring catheter positioned under the inferior nasal turbinate and a reference bridge fomed by a subcutaneous neddle in the forearm, which is isoelectric with the submucosal space of the nasal epithelium. 8 healthy and 9 CF patients were measured each in both nostrils using a standardised superfusion protocol. Superfusion (1ml/min) started with PBS, followed by amiloride (10^{-4} mmol) and Cl-free solution containing amiloride. C6-Ceramide was dissolved in 98% ethanol and added to the Cl-free solution(final ceramide concentration 100 µmol). The epithelium was perfused for 30 min. In the last step ceramide was replaced by isoprenaline. To determine the ceramide effect, ethanol without ceramide was added to the Cl-free solution in 5 controls.

Results: Superfusion of the nasal epithelium with ceramide showed a depolarisation effect in CF (mean ± SD) 4.7 mV ± 7 mV vs 1.2 mV ± 9.3 mV in controls. Ethanol without ceramide showed a hyperpolarisation in controls (mean ± SD) 3.1mV ± 7.1 mV.

Discussion: Superfusion of the nasal epithelium with ceramide could not restore the electrophysiological abnormalities caused by the CFTR defect CFTR-independent activation of ORCC by ceramide is shown in cell attached patch clamp experiments in lymphocytes, but not in respiratory epithelia in vivo.

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Towards zero prevalence of chronic Pseudomonas aeruginosa infection in pediatric patients

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Data from the Belgian Cystic Fibrosis Registry consistently show that in one of the 7 Belgian cystic fibrosis reference centres, the prevalence of *Pseudomonas aeruginosa* (Ps a) (last respiratory culture of the year) has stood at around 25% for several years, roughly half that observed at the national level. They also suggest that a specific antibiotic treatment strategy might have contributed to this particularity.

We aim to report the characteristics of non transplanted CF patients in our clinic, particularly as regards their bacteriological status. Chronic infection by Ps a is defined according to Lee et al. (J Cyst Fibros 2003;2: 29–34).

At the end of 2003, the prevalence of Ps a is 20.7% (n=116). The chronic colonization rate is 19.8 % but only 2.8% in patients aged under 18 (n=72). Serologic data are in agreement with these findings. Most pediatric patients (95%) are prescribed inhaled antibiotic therapy, at least on an intermittent basis, even tough Ps a had never been isolated from the respiratory tract in the majority of them (54%). The spirometric parameters of patients aged between 6 and under 18 are particularly encouraging (average FEV1 : 94% pr., FEV1 ≥ 90% pr.: 70%, FEV1 < 40% pr.: 0%).

We have reported a distinctly low rate of chronic colonization by Ps a in pediatric CF patients and believe that a strategy of early, often « prophylactic » use of low-dose inhaled antibiotics, progressively implemented for over 15 years has greatly contributed to these results. This policy is to some extent similar to the experience reported by Heinzl et al. (Pediatr Pulmonol. 2002;33:32-7). Given the major impact of chronic Ps a colonization on prognosis in CF, it is suggested that a large prospective study of this approach is warranted.

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Pulmonary Function and Pseudomonas aeruginosa colonization in Pediatric CF patients after aggressive treatment of Pseudomonas aeruginosa "First Growth"

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Pseudomonas aeruginosa (Pa) is a common respiratory pathogen in individuals with Cystic Fibrosis (CF), eventually colonizing most CF patients. The presence of Pa in CF is associated with significantly greater decline in pulmonary function and increased need for hospitalization. For the past decade, we have followed an aggressive treatment protocol for "First Growth" of Pa in respiratory cultures from patients attending our paediatric (ages 0-18yr) CF clinic, using 2 weeks iv Piperacillin + Tobramycin, followed by 3 weeks of oral Ciproflaxacin + 3-6 months of nebulized colistin. We have reviewed the results of this approach in our clinic patients (n=124-140). Mean age of Pa "First Growth" was 7.8 years (range 6 mos to 16 yr). Success rate for Pa clearance was 85%. As a result of this intervention, the percentage of Pa colonized CF children attending our clinic has decreased from 44% in 1995 to 14% in 2004. We have reviewed the effect of this treatment protocol on pulmonary function. The overall mean FEV1 for all children attending our CF clinic, aged 6-17 (n=90) is 89.6% predicted, and annual decline in FEV1 –1.45% per year. For those chronically colonized with Pa (n=18), annual decline in FEV1 was –3.09% compared to –0.76% for the Pa negative group. In the Pa negative group, those who had never grown Pa had a mean FEV1 of 93.7% and an annual change of +0.1%, whereas the group who were cleared of Pa following treatment, the mean FEV1 was 95.5% predicted and annual change –1.34%. We conclude that close surveillance and aggressive treatment of Pa in CF patients can decrease the prevalence of chronic colonization and favourably affect pulmonary function.

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Seasonal variation in the number or the severity of pulmonary exacerbations in adult CF patients

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Aim of study: The aim of this research is to determine any seasonal variation in the frequency and severity of pulmonary exacerbations in adult CF patients in our centre.

Patients and methods: This is a retrospective study. Exacerbations over 5 years from January 1999 to December 2003 were recorded. Exacerbations were considered to be severe when intravenous antibiotics were needed and mild when oral antibiotics were given. Data on age, sex, FEV1 and performance score were obtained. Routine or per-operative antibiotics were excluded from the analyses. The year was divided into 'hot seasons' from April to September and 'cold season' from October to March. Patients were divided into two groups according to their general performance score; group 1 had good performance score and group 2 had worse performance status.

Results: Data on 72 patients were investigated. Data on 59 patients were deemed to be sufficient for analysis. Patients in group 2 experienced greater number of both mild and severe exacerbations than group 1 ($P<0.01$ for each). There was no statistical difference of the number of exacerbations during cold seasons compared to those during hot seasons for either group. Age, sex and FEV1 did not affect the seasonal variation in exacerbations.

Conclusion: The present study demonstrates that there is no seasonal variation in the frequency or the severity of pulmonary exacerbations in CF patients irrespective of markers of disease severity. The manpower and bed resources in our centre need to be equally available throughout the year.