The Importance of early Diagnosis in A1AD and the Augmentation Therapy

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Why a Speaker from Essen?

• Since 1985 the Ruhrlandklinik was engaged in the studies of Prolastin
• the chief of the department, N. Konietzko, was the principal investigator
• M. Wencker et al. asked and answered: Does A1A-augmentation therapy slow the annual decline in FEV1 in AAD? (ERJ 97)
A1AD - a genetic Disorder

• Beside Cystic Fibrosis, A1AD is the most common genetically fixed lung disease
• You find one PIZZ typ child among 8,000 newborn in Europe with differences between the countries
• Cystic fibrosis 1:4,000-5,000
• only 10% of all PiZZ are diagnosed
From Genom to Disease

• The genetic abnormality alone is the reason for the development of liver disease in the newborn or child and also for the rare form of necrotising panniculitis

• Lung disease, especially lung emphysema develops in combination with co-factors such as smoking, recurrent infections or toxic agents in the working place
Pathophysiology

• Main problem is the imbalance of proteases and antiproteases within the alveoli, small airways and the lung tissue

• many other inflammatory processes are influenced by the lack of A1A and contribute to the rapid progress of lung and airway damage
Consequences

• We need to diagnose the disease as early as possible to prevent the „Alphas“ from the unnecessary problems
• we have to stop the decline of lung-function in order to have the patient in a better physical condition
• we have to treat them intensively
First Example - Lost Chance

• 35 yrs old male at time of diagnosis
• lung-function was measured for a certificate for his sports
• shortness of breath on exertion was first reported 4 yrs before the final diagnosis was made
• no coughing or wheezing was reported
• no increased numbers of infections
Lung-function Time-Table
What went wrong?

- The doctor didn`t mind for the decline of IVC and FEV1 (300ml/2 years)
- the loss of lung-function was too high
- it would have been necessary to examine blood for the lack of A1AT
- especially smoking cessation could have been started years ago as well as vaccination and inhalation of brochodilators
Correct Procedures in this Case:

- A1AT Serum-Test, genotyping
- lung function test: spirometry, bodyplethysmographie, blood-gasanalysis at rest and on exertion, TLCO
- perfusion scan of the lung, characteristic with defects in the lower parts of the lung
- CT-Scan (bullae, bronchiektasis)
- screening of family members
Therapeutic Procedures

- smoking cessation at once and forever
- inhalation (LABA, ICS, vagolytics)
- pulmonary rehabilitation: in Germany primarily in specialised clinics, later the Alpha continues as an out-patient
- vaccination (pneumococci, influenza)
- detailed information about the disease
- augmentation therapy (60mg/Kg BW)
What about Reality?
Second Example

• 41 ys old male
• 25 ys of active smoking
• shortness of breath on exertion since 6 ys
• recurrent broncho-pulmonary infections
• oedema since 4 weeks (lower limbs)
• no shortness of breath at rest
Former Diagnosis: Asthma

• 2 y ago, he visited his doctor: Asthma was diagnosed by lung function test with a positive broncholytic result. The documented spirometry was not found!!

• patient never had shortness of breath at rest, no wheezing at night

• no history of rhinitis, eczema or other allergic diseases
Clinical Findings

• underweight patient (1,72m/58 kg)
• shortness of breath when unclothing
• cyanosis
• oedema of the lower limbs
• silent chest on auscultation
• BGA: pO2 54mmHg, pCO2 47mmHg
1. Ganzkörperplethysmographie

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Kommentar:
Diff.-Messung ist bei der erheblichen Atemnot nicht möglich!
Therapeutic Procedures

• Smoking cessation, improve nutritional status
• LABA, ICS, vagolytics, diuretics
• longterm oxygen-therapy
• polysomnography and capnography
• non-invasive ventilation?
• No augmentation therapy (lungfunction!!)
• rehab. and listing for lung-transplantation
What Do we Gain by Therapy?

• High influence of smoking cessation: Delta FEV1 smo. 132ml/y smo.qu. 58ml/y
• Bronchodilators: improve FEV1, but good response is correlated with a higher decline of FEV1 on a longterm base
• reduction of exacerbations by vagolytics
• shortening of exacerbations by antibiotics
• better physical status by rehabilitation
Why early Detection?

- The prognosis correlates with the FEV1
- the first parameter changing in the natural course of the disease is TLCO, due to the reduction of alveolar surface (in the 20s)
- CT-densitometry reveals the tissue damage in the 30s-40s
- spirometry changes in the 30s to 40s
Influence of FEV1

• The main decline of FEV1/y was observed between 35-65% pred.
• The decline was lower in patients with higher and lower FEV1
• mortality of the disease is high below an FEV1 of 35% pred.
How can we find the early Stages?

• patients are symptomatic in a moderate advanced stage, because they do not need their lung reserves under normal conditions

• we have to intensify the use of lung function tests among physicians
The Role of Smoking in A1AD

• Larsson (1978) reported an median life expectancy of 40y for smokers and 65y for never smokers

• never smoking PiZZ preserve a normal lung function until an age of 50y
What has to be done?

• we must teach the general practitioners. There are good guidelines which answer the question: When do you have to look for the A1A- deficiency?

The motto of Talecris is “Think of it!“

• when we have identified an index person, we must test his relatives (in DK 25, in Germany only 5-7 examinations)
ATS/ERS-Guidelines
When to test for A1AD?

- an emphysema below the age of 40y or non-smoking patients
- COPD or asthma with negative results of bronchodilator application
- patients with unknown liver disease
- bronchiektasis
- Wegeners disease
Do you have to repeat the Test?

• The result in a stable phase without an exacerbation of COPD must not be confirmed
• exacerbation leads to a higher level even in patients with AAD, so you must test again
• in unclear cases pheno- and genotyping is necessary
Consequences

• if all doctors follow the guidelines we can expect increasing numbers of tests for AAD
• we could identify patients with mild or moderate disease offering the chance of better preservation of lung-function
• we have to increase the number of lung-function tests to a level of the ECG
Augmentation Therapy

- from the beginning the idea of substitution of the lacking enzym was in the heads of the clinicians dealing with these patients
- like a diabetic person who does not have enough insulin the application of A1A was the aim
- purified A1A from pooled plasma was produced and tested in the early eighties
Augmentation: Different Types

- i.v. infusion 60mg/kg BW once weekly
- i.v. infusion 250mg/kg BW once monthly
- inhalation of 50-100 mg once daily via high tech nebulizer
- recombinant AA (shepmilk) once weekly i.v.
Intravenous Therapy

• The i.v. infusion leads in the before mentioned dose to a sufficient level in the alveoli and in the epithelium-lining-fluid
• only 3% of the infused drug reach these compartments and can neutralise the aggressive elastase
Our Experience in Germany

- We always administered 60mg/kg BW and collected data from 443 patients (87-95)
- the therapy was well tolerated
- only 3 patients stopped therapy because of intolerable sideeffects
- clinical examination, lungfunction tests and laboratory test were performed twice a year
Results

- In comparison to an untreated Danish group, the decline in FEV1 was lower in the subgroup of a FEV1 30-65% pred.
- The number of exacerbations was lower.
- Although it was not a placebo-controlled study, the augmentation therapy is part of the therapy in some countries.
Additional Studies

• You will hear about the EXACTLE-study, placebo-controlled, published in 2008
• there is an ongoing study with another AA-preparation (Zemaira), placebo-controlled and double-blinded, very similar to the EXACTLE-study
• we expect results in 2010
Specialisation is necessary

- pneumologists should be trained in order to give optimal advice
- specialised centres for AAD are founded all over Germany
- we need more centres for children and patients with liver disease
Summary

• there is still much work to be done to spread information about the disease
• we have a lot of drugs to treat the developing airway disease
• augmentation therapy seems to improve the outcome of a well defined subgroup regarding our experience in Germany since 20 ys