Screening for alpha\textsubscript{1}-Pi deficiency in patients with lung diseases

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Introduction

Alpha\textsubscript{1}-Pi deficiency is a widely under-recognized disease. In most European countries and in the U.S.A., it is estimated that only 5–10\% of individuals with severe deficiency are identified. This, however, hampers necessary lifestyle changes to be made, such as smoking cessation, occupational changes and genetic counseling for couples at risk. The WHO recommended intensified testing and suggested that patients with COPD and asthma should be screened for $z_1$-Pi deficiency (1). This is based on data in which 2–3\% of patients with COPD were found to be homozygous for the most common $z_1$-Pi deficiency allele PiZ (2). The WHO recommended that ‘...all patients with COPD and adults as well as adolescents with asthma should be screened once in their life for $z_1$-antitrypsin deficiency, using a quantitative test’ (i.e. an immunoassay). Patients with abnormal results on the quantitative test should then undergo Pi typing to identify the phenotype.

On the basis of this recommendation, we planned a study in which a large outpatient population of COPD and asthma patients were screened for $z_1$-Pi deficiency in seven private practices. The aim of this study was to identify the frequency of $z_1$-Pi deficiency in a target population in Germany using a dried blood spot test for $z_1$-Pi levels and isoelectric focusing (IEF). This allowed us to evaluate the feasibility of collecting large numbers of samples with this method and the shipment abroad.

The advantage of using the dried blood spot method with small amounts of blood was the lack of need for a skilled phlebotomist. Sampling and handling is also greatly improved and transportation of these samples can be easily done by regular mail with no refrigeration required.

Methods

We recruited patients from three pneumologists and four general practitioners in, or close to, Essen, Germany, and looked at their $z_1$-Pi levels and phenotypes. Patients with COPD, pulmonary emphysema, asthma or bronchiectasis were recruited and demographic data was collected. Patients gave informed consent and samples were either taken from the hyperemic earlobe or from a finger and placed on the filter paper. Included was a questionnaire recording data on smoking history, symptoms and diagnosis. Dried blood spots were then transported to and analyzed at the AAT Deficiency Detection Center in Salt Lake City, UT, U.S.A.

A defined volume of filter paper was used to elute serum for the quantitative $z_1$-Pi levels. Similarly, dried blood spots were used to elute either $z_1$-Pi protein for IEF or DNA for genotyping. In this study, IEF was carried out on all samples regardless of serum $z_1$-Pi levels to determine the frequency of heterozygotes. In the case of equivocal results some samples required additional genotyping.

Results

More than 1000 samples were collected in a short period of time. The quality of the blood spots was excellent in most cases. Any problems with the samples was usually caused by not spotting carefully. In these cases the amount of blood on the filter paper was too small to do a quantitative analysis. In a vast majority of the cases there was enough dried blood to do $z_1$-Pi levels and phenotypes. No problems were encountered with the shipment of samples.

The mean patient age was 52 years, with a wide scattering, and about half of the patients were male. A proportion were ex-smokers but, surprisingly, more than 40\% were non-smokers. The ratio of relatives with known $z_1$-antitrypsin deficiency was very low. The patient usually reported to their doctor’s office because of dyspnoea on exertion. A large proportion had chronic cough and phlegm, asthmatic attacks and wheezing. The physicians’ diagnosis given for these patients was more than 40\% asthma, 35\% chronic obstructive bronchitis, 27\% emphysema and more rarely, chronic bronchitis, acute bronchitis and a few patients with bronchiectasis. Even though the analysis of the samples is not complete, the preliminary results show a percentage of homozygous PiZ of significantly less than 1\% which are lower than the expected 2–3\%, according to previous results (2). A few samples are being genotyped because of equivocal findings, with results still pending.

In conclusion, the participating physicians did a very good job recruiting patients with COPD and asthma as recommended by the WHO. In general, few problems were encountered sampling the blood spots and transatlantic shipping did not compromise the quality of the samples. The dried blood spot test was very well-suited to do large scale screening; however, the identification rate in this patient sample seems to be lower than previously reported.
References
