

## LETTERS

# Plasma levels of TIMP-1 are higher in 34-year-old individuals with severe $\alpha$ 1-antitrypsin deficiency

$\alpha$ 1-Antitrypsin (AAT) is one of the major proteins in the circulation eliciting significant protection against activated serine proteases, such as neutrophil elastase and proteinase-3. Moderate and severe AAT deficiency (AATD) is almost entirely caused by the Z (Glu342 to lysine change) and S (Glu264 to valine change) alleles as opposed to the normal wild-type M allele. Severe ZZ deficiency of AAT, characterised by a decrease in serum AAT levels to values <20% of normal, entails a high risk of developing pulmonary emphysema. This fact provides the rationale for the protease–antiprotease imbalance theory of the pathogenesis of emphysema.

We hypothesised that in subjects with AATD, other protease inhibitors may mitigate the deficiency of AAT, and ensure the normal growth and function of the lung from childhood to early adulthood. In a previous reports focusing on plasma markers of the serine protease–antiprotease balance, we have shown that 18-year-old ZZ and SZ AATD subjects, identified in the Swedish neonatal AATD screening of 1972–1974, had significantly higher plasma concentrations of  $\alpha$ 2-macroglobulin and  $\alpha$ 1-antichymotrypsin, and lower levels of neutrophil lipocalin, a marker of neutrophil activity.<sup>1</sup> Interestingly, at the age of 26 the same ZZ and SZ AATD subjects had significantly higher plasma secretory leucocyte protease inhibitor and, again, lower neutrophil lipocalin levels, compared with age-matched controls.<sup>2</sup> At the 30-year check-up, these discrepancies were not confirmed.<sup>3</sup>

In this study we wanted to investigate whether there is any relationship between circulating plasma levels of AAT and tissue inhibitor of metalloproteases-1 (TIMP-1), an important inhibitor of metalloproteases (MMPs) that plays a role in the pathogenesis of emphysema.<sup>4</sup> The study cohort included the above-mentioned 34-year-old AATD subjects (ZZ, n=50; SZ, n=22) and 84 age-matched controls with normal AAT concentrations. As shown in table 1, plasma levels

of AAT in the subjects were ranked MM>SZ>ZZ and were different among the groups (p <0.001). The levels of C-reactive protein, a general marker of inflammation, were normal in all three groups. The mean (95% CI) level of plasma TIMP-1 was 135.8 ng/ml (114.1 to 157.5) in the ZZ group, 99.4 ng/ml (74.97 to 123.8) in the SZ group and 65.3 ng/ml (56.99 to 73.59) in the MM group. Thus, plasma levels of TIMP-1 were higher in the ZZ (52.1%, p <0.001) and SZ group (27%, p <0.05) as compared with the controls. Linear regression analysis revealed an inverse relationship between levels of TIMP-1 and AAT (r=−0.459, p <0.001) (figure 1, supplementary data). Notably, the elevated TIMP-1 and its negative correlation with AAT levels were not related to the levels of C-reactive protein.

Previous studies in which TIMP-1 was analysed showed that under normal conditions the TIMP-1 levels outweigh MMPs, tipping the balance in favour of protease inhibitors.<sup>5</sup> We therefore think that higher levels of TIMP-1 in young adults with AATD might provide a compensatory mechanism in maintaining the protease–antiprotease balance and blocking the destructive potential of proteases. We hope this finding opens a new window for further studies on the role of TIMPs/MMPs in the pathogenesis of AATD-related emphysema.

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## Identifying supportive and palliative care needs in people with a recent diagnosis of thoracic cancer: acceptability of the SPARC questionnaire

National guidelines recommend that physical, psychological, social, spiritual and financial support needs are routinely assessed in people with lung cancer, as a minimum, around the time of diagnosis, on completion of primary treatment, when there is significant deterioration of symptoms and when dying is diagnosed.<sup>1 2</sup> Self-assessment is considered a useful part of the process and several tools have been highlighted.<sup>3</sup> One of these, the Sheffield Profile for Assessment and Referral to Care (SPARC), contains 45 questions with 56 possible responses covering seven areas of potential need.<sup>4</sup> For most questions, patients rate the degree to which they have been distressed or bothered by a symptom or issue in the past month using the responses: 0 'Not at all', 1 'A little bit', 2 'Quite a bit' and 3 'Very much'. However, because there are no reports of its

**Table 1** Study groups and plasma concentrations of  $\alpha$ 1-antitrypsin (AAT), C-reactive protein (CRP) and tissue inhibitor of metalloproteases-1 (TIMP-1)

Study group	Number	Males/females	AAT (mg/ml) mean (SD)			CRP (mg/ml) mean (SD)			TIMP-1 (ng/ml) mean (SD)		
			Total	Males	Females	Total	Males	Females	Total	Males	Females
MM	84	29/55	1.28 (0.36)	1.22 (0.3)	1.32 (0.3)	2.12 (3.3)	1.39 (2.17)	2.5 (3.7)	65.3 (38.3)	59.5 (33.7)	68.3 (40.4)
SZ	22	12/10	0.601*** (0.11)	0.58 (0.09)	0.64 (0.13)	1.4 (2.2)	1.82 (2.7)	0.92 (1.24)	99.4* (55.1)	113.5 (69.1)	82.4 (25.6)
ZZ	50	31/19	0.225*** (0.08)	0.23 (0.06)	0.23 (0.11)	2.1 (2.2)	2.56 (2.56)	1.99 (1.6)	136.4*** (75.2)	150.4 (84.9)	112.1 (53.9)

\*p<0.05 and \*\*\*p<0.001 show significant difference between ZZ or SZ AAT deficiency and controls with the normal MM genotype of AAT.

**Table 1** Appropriateness and free-text feedback

Was the questionnaire appropriate? (n)	Free-text comments made (n)	Comments (n with similar theme)
Yes (83)	16	Positive comments regarding the questionnaire, eg good questions, simple to complete, comprehensive (6). Given too early, not started treatment yet (5). Response options in communication and information issues not clear (2). Good that I did not have to answer questions I did not want to. Difficult to complete because of small print. Specific questions considered inappropriate; sexual function (spouse in nursing home); religious needs (atheist). Unspecified questions considered potentially upsetting to patient by spouse completing questionnaire.
Left blank (14)	3	Not started chemotherapy yet which may alter the response (2). I may have different answers on different days.
No (3)	1	Not had any treatment yet, or know the extent of my illness.

use in patients with a recent diagnosis of thoracic cancer, before adopting it locally, we have surveyed its acceptability.

Patients within 4 weeks of their diagnosis of thoracic cancer attending outpatient clinics were identified. After obtaining verbal consent, patients were asked to complete the SPARC questionnaire, if necessary with the help of a carer or the member of staff in attendance, with the instruction to leave any questions they were unsure of blank. On completion, they were asked to record on a separate feedback form if they felt the questionnaire was appropriate, had any comments about the questions asked or had any other comments. The results were collated anonymously and analysed using descriptive statistics, with comments relating to the questionnaire grouped into themes. The survey was registered with the Trust Governance and Health Audit department (no. 775).

Of those approached, 86% agreed to take part, with data from 100 patients analysed (63 male; mean (SD) age 68 (9) years; non-small cell lung cancer 70, small cell lung cancer 20, mesothelioma 10; all Caucasian, with English as the first language in 98). Questionnaires were completed by the patient alone, or with the aid of a member of staff or carer in 65, 22 and 8 instances, respectively. Of the maximum 56 responses, the median (IQR) number completed was 52 (47–54). The questionnaire was considered appropriate by 83 patients, not appropriate by 3, and 14 did not answer this question. Of 22 comments made, only one related to some questions being potentially upsetting (table 1). Patients had a median (IQR) of 2 (0–5), 4 (2–7) and 8 (5–12) symptoms or issues which distressed or bothered them 'very much', 'quite a bit' and 'a little', respectively. Most common were feeling tired, shortness of breath and problems sleeping at night.

Our results suggest that the SPARC questionnaire is acceptable to the majority of patients with a recent diagnosis of thoracic cancer. A clear explanation of the purpose of the questionnaire, the instruction to leave a question blank when unsure and the offer

of help to complete it, taken up by about a fifth of patients, may all have contributed to its acceptability. On the basis of our results, we have introduced the SPARC into routine practice, having increased the text size to improve readability.

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## An outbreak of H1N1 influenza in a respiratory unit

Pandemic influenza A (H1N1) is a major global public health concern.<sup>1</sup> We report an

outbreak of H1N1 influenza involving clinical staff and patients in a teaching hospital in the North East of Scotland.

In October 2009, a teenage patient was admitted with an exacerbation of asthma. As there was no reason to suspect H1N1, the patient was not isolated. However, nose and throat swabs were in fact taken on the day of admission and were positive for H1N1 by PCR within 24 h. At this point, source isolation precautions were instituted. Seven otherwise healthy clinical staff in our department (6 doctors and 1 nurse; mean age 29, three males) subsequently developed typical symptoms within the next 9 days. Cases were confirmed by viral PCR from pooled nasal and throat samples. As H1N1 was common in the community at this time, it was not possible to determine whether the patient was the source of infection; however, five of the affected clinical staff had been in direct contact with the patient and the first symptoms reported by them were 48 h following his admission to the ward.

Affected staff were advised to remain off work for a week after the initial onset of their symptoms; 33 working days were subsequently lost due to illness. The cumulative number of staff members infected with H1N1 virus in our unit over a week from the time of first symptoms reported by a member of staff is shown (figure 1). During the same period, six patients on the ward also tested positive for H1N1 after developing flu-like symptoms. In two of these, H1N1 was likely to have been contracted while in hospital as they had been admitted several days earlier and were recovering from their presenting illnesses.

Our experience has demonstrated that within the hospital environment, H1N1 is readily and rapidly transmissible between individuals. This outbreak highlights the importance of rapidly identifying infected patients and instituting source isolation procedures. Moreover, it is imperative that members of hospital staff use appropriate protection equipment and receive H1N1 immunisation (as recommended by the Department of Health) at the earliest opportunity. This should reduce the risk not only of healthcare workers contracting the virus from infected patients, but also of cross-infection between other patients and other healthcare workers. It is important that hospital trusts recognise the potential impact of H1N1 on frontline staffing and ensure appropriate contingency plans are made.

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