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Neurone-specific enolase levels in pleural effusions in patients with rheumatoid arthritis

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Abstract

***Background* – High pleural fluid levels of neurone-specific enolase (NSE) have been reported, not only in patients with small cell lung cancer but also in those with chronic inflammatory diseases.**

***Methods* – NSE concentrations were determined in pleural fluid and serum from 342 patients with pleural effusions including 17 with rheumatoid arthritis.**

***Results* – The median NSE concentration in pleural fluid was higher in rheumatoid effusions than in any other condition studied. The median pleural fluid:serum NSE ratio was highest in patients with rheumatoid arthritis (11·6) and about unity in all other diseases including small cell lung cancer (0·9). In patients with rheumatoid arthritis pleural fluid concentrations of NSE correlated inversely with pleural fluid glucose concentrations and the pH of the pleural fluid.**

***Conclusions* – A high pleural fluid:serum NSE ratio was found consistently in pleural effusions from patients with rheumatoid disease.**

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Keywords: neurone-specific enolase, pleural effusion, rheumatoid arthritis.

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Neurone-specific enolase (NSE) is a glycolytic enzyme which occurs mainly in neuronal and neuroendocrine cells.[1 2] Many neuroendocrine tumours stain for NSE, and high serum levels occur in patients with small cell lung cancer.[3]

Raised concentrations of NSE in pleural fluid have been shown to differentiate pleural effusions due to small cell lung cancer from effusions of other origin,[4] but increased concentrations of NSE in pleural fluid have also been reported in some chronic inflammatory diseases such as rheumatoid arthritis.[5] We determined pleural fluid and serum levels of NSE in 342 patients with pleural effusions of various aetiologies including 17 with rheumatoid arthritis.

Methods

Pleural fluid and blood were collected from 342 patients with a newly detected pleural effusion. Since haemolysis causes an increase in the levels of NSE, patients with haemorrhagic pleural effusions were excluded. The patients were divided into the following 10 diagnostic categories: rheumatoid arthritis, in accordance with the 1987 revised criteria of the American College of Rheumatology (ACR) (n = 17, all were seropositive with respect to rheumatoid factor and in four cases pleurisy was the first manifestation of the disease); lung cancer (n = 52, 12 with small cell lung cancer); malignant mesothelioma (n = 10); cancer of extrapulmonary origin (n = 67); systemic lupus erythematosus (SLE) in accordance with the ACR criteria for the classification of SLE (n = 5); microbiologically or histologically verified tuberculosis (n = 27); parapneumonic effusion or pleural empyema (n = 43); other defined diseases (n = 22); exudative pleural effusion of unknown aetiology (n = 72); and congestive heart failure with transudative pleural effusion (n = 27).

NSE was measured with a commercially available double antibody radioimmunoassay (Pharmacia AB, Uppsala, Sweden). The statistical calculations were performed using the Mann-Whitney's test and Spearman's correlation test.

Results

The median NSE concentration in pleural fluid was higher in the effusions due to rheumatoid arthritis than in those due to any other disease (table 1). In rheumatoid arthritis NSE concentrations in the pleural fluid correlated inversely with pleural fluid concentrations of glucose (Spearman's $r = -0·49$) and the pH of the pleural fluid ($r = -0·61$). The median pleural fluid:serum NSE ratio was much higher in rheumatoid arthritis than in any of the other diagnoses (table 2).

Although the concentration of NSE in the pleural fluid was higher in effusions associated with small cell lung cancer (median 18·1 μg/l; range 1·8–107·6, 95% confidence interval (CI) 5·1 to 30·8) than in other lung cancers (median 5·4 μg/l; range 2·5–168·8; 95% CI 4·4 to 7·0; p = 0·05), it was still lower than in the

Table 1 Pleural fluid concentrations of neurone-specific enolase (NSE) (μg/l) in rheumatoid pleural effusions compared with effusions of other aetiologies

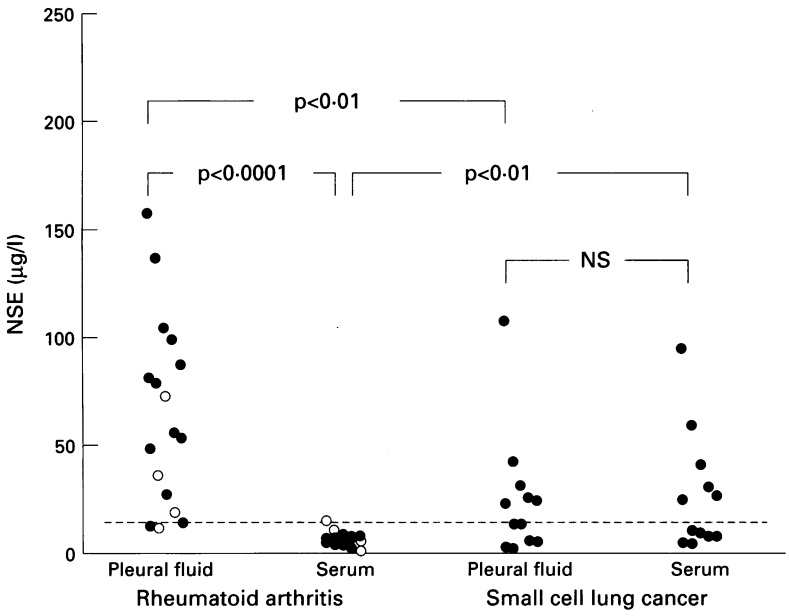
Diagnosis	*n*	*Median*	*Range*	*95% CI*	*p**
Rheumatoid arthritis	17	56·2	12·2–157·8	19·3 to 99·4	
Lung cancer	52	6·1	1·8–168·8	4·7 to 10·3	<0·0001
Mesothelioma	10	7·6	1·3–52·6	2·9 to 40·7	<0·001
Other cancers	67	6·5	0–202·0	4·9 to 9·5	<0·0001
SLE	5	3·3	2·5–12·4	–	<0·005
Tuberculosis	27	7·1	1·6–116·8	3·3 to 12·3	<0·0001
Parapneumonic effusions	43	4·9	0·5–31·3	3·6 to 7·3	<0·0001
Other verified diagnoses	22	3·9	1·1–51·7	2·3 to 5·1	<0·0001
Non-specific effusions	72	5·1	1·0–23·0	4·3 to 5·6	<0·0001
Congestive heart failure	27	2·7	1·0–12·0	2·0 to 3·2	<0·0001

SLE = systemic lupus erythematosus.
* p values versus rheumatoid arthritis (Mann-Whitney test).

Table 2 Pleural fluid:serum neurone-specific enolase (NSE) ratios in rheumatoid pleural effusions compared with effusions of other aetiologies

Diagnosis	*n*	*Median*	*Range*	*95% CI*	*p**
Rheumatoid arthritis	15	11·6	1·2–81·0	3·1 to 24·7	
Lung cancer	52	0·9	0·1–21·1	0·6 to 1·1	<0·0001
Mesothelioma	10	1·4	0·2–9·9	0·6 to 6·8	<0·005
Other cancers	66	0·9	0–12·0	0·6 to 1·1	<0·0001
SLE	2	1·9	0·7–3·2	—	NS
Tuberculosis	26	0·8	0·1–10·7	0·5 to 1·7	<0·0001
Parapneumonic effusions	43	1·0	0·2–4·4	0·7 to 1·4	<0·0001
Other verified diagnoses	22	0·6	0·1–6·0	0·4 to 0·9	<0·0001
Non-specific effusions	70	0·9	0·1–5·7	0·7 to 1·2	<0·0001
Congestive heart failure	27	0·3	0·1–3·6	0·2 to 0·5	<0·0001

SLE = systemic lupus erythematosus.
* p values versus rheumatoid arthritis (Mann-Whitney test).



Pleural fluid and serum levels of neurone-specific enolase (NSE) in patients with rheumatoid arthritis and small cell lung cancer. Patients with pleurisy as their first manifestation of rheumatoid arthritis are indicated by open circles. Dotted line = upper reference limit for serum NSE (Mann-Whitney test).

effusions due to rheumatoid arthritis (figure). The pleural fluid:serum NSE ratio was much higher in rheumatoid arthritis than in small cell lung cancer (median 0·86; range 1·1–10·5; 95% CI 0·4 to 1·2; p <0·01).

Using 2·4 as the cutoff value, the pleural fluid:serum NSE ratio had a sensitivity of 87% and a specificity of 84% for the diagnosis of rheumatoid arthritis. The specificity increased to 91% when the cancers were excluded.

Discussion

We observed remarkably high NSE concentrations in rheumatoid pleural effusions which distinguished rheumatoid pleurisy from any other non-malignant inflammatory disease and from neoplastic diseases. There was a considerable overlap in the pleural fluid concentrations of NSE between patients with rheumatoid arthritis and those with small cell lung cancer, but the significantly increased pleural fluid:serum NSE ratio differentiated those with rheumatoid arthritis from those with small cell lung cancer.

Diagnostically useful characteristics of a rheumatoid pleural effusion include a low glucose concentration, a low pH, a high lactate dehydrogenase level, and low complement concentrations.[6] However, none of these tests is sensitive and specific enough for a specific diagnosis of rheumatoid effusion, and they should be considered within the clinical context. The diagnosis of rheumatoid pleurisy may be particularly difficult when a pleural effusion is the first manifestation of rheumatoid arthritis. In the present study pleural fluid concentrations of NSE, and, particularly, the pleural fluid:serum NSE ratio, were useful for identifying patients with rheumatoid arthritis, including those without joint disease. However, we do not regard the determination of pleural fluid levels of NSE as being superior to the traditional laboratory tests used in the diagnosis of rheumatoid pleurisy.

The high pleural fluid:serum NSE ratio suggests local release and accumulation of NSE within the pleural space in rheumatoid pleurisy. Neuroendocrine cells are not found in the pleural membrane, and the neuroendocrine cells of the lung are thought to produce NSE in response to hypoxaemia.[7] A low oxygen tension, high carbon dioxide tension, low glucose level, high lactate level, and low pH occur in both synovial and pleural effusions in rheumatoid arthritis,[8–10] oxygen tensions of 3–6·5 kPa having been reported in rheumatoid pleural effusions.[9,11] In rheumatoid pleurisy, inflammation and thickening of the pleura and local vasculitis might be the cause of this hypoxaemia and increased anaerobic glycolysis. Accumulation of the products of anaerobic glycolysis (carbon dioxide and lactate) might account for the pleural fluid acidosis. Our observation that NSE levels in rheumatoid pleural effusions correlated inversely with glucose levels and pH suggests some relationship between high NSE levels and anaerobic glycolysis. It is possible that the high NSE concentrations in rheumatoid pleural effusions are associated with local tissue hypoxaemia and subsequent increased anaerobic glycolysis.

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Epidemic outbreak of interstitial lung disease in aerographics textile workers – the "Ardystil syndrome": a first year follow up

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Abstract

Background **– The longer term respiratory effects of massive inhalational exposure of textile printing sprayers to Acramin (the "Ardystil syndrome") are not well established.**

Methods **– A 12 month follow up of 27 heavily exposed textile sprayers was performed.**

Results **– Twenty one patients experienced cough, 18 dyspnoea, and 17 nose bleeding at initial exposure, with histological evidence of organising pneumonia in 13 cases, radiological abnormalities detected by computed tomographic scanning in 20 cases, and diminution of diffusion capacity to below 80% of predicted in seven cases. At one year after exposure symptoms persisted in 15 cases, radiological alterations in six, and diffusion capacity was reduced in nine.**

Conclusions **– Whilst most of our patients showed improvement at one year, evidence of persistent lung involvement was present in an appreciable minority of exposed cases.**

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Keywords: occupational lung disease, interstitial lung disease.

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An epidemic outbreak of interstitial lung disease occurred in textile print spraying companies in the Autonomous Community of Valencia, Spain in 1992.[1 2] During that year six workers died of a restrictive pulmonary insufficiency due to organising pneumonia associated sometimes with pulmonary fibrosis, and another worker proceeded to double lung transplantation. This has been called locally the "Ardystil syndrome", after the name of the firm in which the first deaths occurred. Investigations carried out by the Public Health Department established that the lung disease was caused by spraying procedures delivering a respirable aerosol of Acramin FWN (a substance obtained from the reaction between a diethylenetriamine and adipic acid).[2] Organising pneumonia is the main pathological feature, but the pathology ranges from non-specific (or minor) lung lesions to pulmonary fibrosis.

In the present study we report the clinical, radiological, and functional courses of patients with this syndrome followed up over a one year period.

Methods

Approximately 90 workers in the Autonomous Community of Valencia are thought to have been affected by exposure, of whom 27 (21 women), including the most severe clinical cases, were treated in our hospital. The mean (SD) age of the patients was 23 (8) years (range 17–52), and 21 were smokers. Eight of these patients were seen specifically for assessment for possible lung transplantation. Diagnosis was confirmed by transbronchial biopsy in 24 cases, videothoracoscopy in one, and at necropsy in another. In one patient the severity of the disease prevented the performance of a pulmonary biopsy. Lung abnormalities were interpreted as minor changes (increased numbers of macrophages) in six cases, intra-alveolar knots of fibrin in eight, and organising pneumonia in 13. All 27 patients were treated with oral corticosteroids.

Results

The most frequently reported symptoms at presentation were cough (21 cases), shortness of breath (18 cases), and nose bleeding (17 cases). After one year these symptoms had significantly improved in the 26 survivors with nose bleeding persisting in one patient, cough in eight, and shortness of breath in four. In addition to the respiratory symptoms, 14 patients experienced abdominal pain, diarrhoea or nausea. Cognitive disorders (memory loss) and minor neurological manifestations (head-