

Pulmonary function abnormalities in children with Henoch–Schönlein purpura

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ABSTRACT: Henoch–Schönlein purpura (HSP) is a widespread necrotizing vasculitis affecting small vessels characterized by nonthrombocytopenic purpura. Pulmonary involvement is a rare fatal complication with diffuse alveolar haemorrhage. The objective of this study was to evaluate possible early lung function abnormalities and to establish any relationship with the clinical activity of the disease.

Fifteen children with HSP and without clinical or radiological evidence of lung involvement underwent pulmonary function study at the onset of the disease. A sample of 28 subjects matched by age, height, and weight was chosen as a control group. After a mean of 21 months (range 12–43) lung function tests were repeated in 10 of the previously studied children.

During the acute phase of the disease the transfer factor for carbon monoxide, measured by steady-state (TL_{COss}) and single-breath (TL_{COsb}) methods, was found to be significantly lower in children with HSP than control subjects. There was no significant relationship between pulmonary function tests with symptoms and signs at onset, nor was there any correlation between variables and serum immunoglobulin A (IgA) concentration. In all but two patients, clinical recovery was observed within 6 weeks from the onset of the disease. In one case relapses of purpuric skin lesions were observed during the first 3 months of follow-up. The second case had relapses of purpuric skin lesions and microscopical haematuria during the 12 months following the onset of the disease with characteristic IgA mesangial deposition on renal biopsy. Although the overall mean value of TL_{COsb} improved from baseline to the second investigation, in both patients the recurrences of clinical signs were associated with a slight impairment of TL_{COsb} at the second evaluation.

These data suggest an early subclinical lung impairment in children with Henoch–Schönlein purpura during the active phase of the disease. The presence of isolated pulmonary function abnormalities was not associated with the subsequent development of lung disease.

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Henoch–Schönlein purpura (HSP) is a widespread necrotizing vasculitis affecting small vessels characterized by nonthrombocytopenic purpura. The histopathological features show leukocytoclastic vasculitis with infiltration of the necrotic vessel wall by leukocytes, and scattered nuclear debris accumulates around the lesions [1]. It is primarily a childhood disorder and occurs mostly between 5 and 15 yrs of age [2–4]. The disease often begins after an upper respiratory tract infection. The presence of palpable purpura is essential to the diagnosis, abdominal pain and arthralgia or arthritis usually occur only in 80% of the cases, and glomerulonephritis develops in ~20–50% of the children [5, 6].

Clinically important pulmonary disease is extremely rare in this condition [7–10]. The cases reported in the literature were fatal and *post mortem* examination revealed pulmonary haemorrhage or infarction secondary to vasculitis. The transfer factor of the lung for carbon monoxide (TL_{CO}) has been shown to be impaired in children with HSP who were

free of clinical pulmonary symptoms [11]. These observations, however, have not been confirmed or refuted by other investigators. Furthermore, the above study included patients with abnormal chest radiographs.

To evaluate possible early lung function abnormalities and any likely relationship with the clinical activity of the disease, respiratory function was studied in a group of paediatric patients with HSP and without clinical or radiological evidence of pulmonary involvement. In a group of unselected children with HSP studied previously, the lung function tests were repeated after a mean interval of 21 months from the first investigation.

Subjects and methods

Patients with Henoch–Schönlein purpura

Criteria for inclusion in the study were: 1) proven HSP; 2) no clinical pulmonary signs and symptoms upon physical

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examination (or history as determined by questioning the children as well as the parents); and 3) normal chest radiograph. Children with histories of pulmonary disease and clinical and/or radiographic abnormalities were excluded from the study.

Among the 30 consecutive children admitted to the authors' Paediatric Department (from October 1992 to April 1994) with the diagnosis of HSP only 19 fulfilled the aforementioned inclusion criteria and were enrolled in the study. Eleven patients were excluded, 10 because of interstitial infiltrate on chest radiography and one because of current asthma. Four patients were unable to perform reproducible tests and were then excluded. Therefore, data analysis was conducted on 15 children. There were eight males and seven females, aged 5–13 yrs (mean \pm SD 7.6 \pm 1.9 yrs). Their mean height was 131 \pm 13 cm (range 113–161 cm) and weight 30 \pm 7.6 kg (range 21–47 kg).

A diagnosis of HSP was established on the basis of clinical evidence of palpable purpura characteristic of the syndrome and not related to thrombocytopenia according to the American College of Rheumatology Criteria for the classification of HSP [12]. All children were untreated before entry to the study, but one underwent corticosteroid therapy (prednisone 1 mg \cdot kg⁻¹ \cdot day⁻¹) after initial evaluation. At the time of admission routine blood samples were collected for the determination of haemoglobin levels, serum immunoglobulins, complement (C3 and C4), antinuclear antibodies (ANA), rheumatoid factor (RF) and circulating immune complexes [13]. In addition, throat cultures and serial urine analyses were performed.

Healthy subjects

Twenty-eight age-matched hospital patients (15 males and 13 females, aged 6–13 yrs; mean \pm SD 8.7 \pm 1.8 yrs) with benign nonthoracic diseases were chosen as a control group. Their mean height was 131 \pm 10 cm (range 114–158 cm) and weight 29 \pm 6.61 kg (range 19–40 kg).

Pulmonary function tests

Pulmonary function tests were performed 1–43 days (10 \pm 11 days) after the onset of the skin rash. Flow–volume curves were obtained with a Jaeger spirometer (Würzburg, Germany) in order to determine forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁). The measurements of residual volume (RV) were determined by the helium dilution technique. Total lung capacity (TLC) was calculated from RV+vital capacity (VC). The pulmonary $\dot{V}_{L,CO}$ was assessed using the steady-state ($\dot{V}_{L,CO_{ss}}$), and single-breath ($\dot{V}_{L,CO_{sb}}$) methods and corrected for haemoglobin level [14]. Test results are presented as mean absolute values as well as the percentage of the predicted value for each patient with the exception of the FEV₁/FVC ratio (FEV₁%). Predicted normal values were obtained from those published by COTES *et al.* [15] and CHAUSSAIN *et al.* [16].

Follow-up studies

After the children were discharged from the hospital, urine was screened once a week during at least the following 3 months or more frequently if indicated. Of the 15 children with HSP studied at time of diagnosis, five were

lost from the second investigation. The remaining 10 patients (six males and four females, aged 5–13 yrs) had lung function tests repeated after a mean of 21 \pm 10 months (range 12–43) from presentation.

Statistical analysis

Results are expressed as mean \pm SD and a p-value <0.05 was accepted as the level of significance. The data distribution was analysed with skewness and kurtosis coefficients. When appropriate a normal distribution was obtained after logarithmic transformation of data with a non-normal distribution. For normally distributed data, the significance was assessed using analysis of variance (ANOVA) and covariance, the Pearson correlation index and t-test for paired samples. For non-normally distributed data, the Pearson correlation index computed on ranks, the Mann–Whitney U-test and the Wilcoxon matched-pairs signed-ranks test were used. Categorical variables were compared between children with HSP and control subjects using the Chi-squared test. The computer program Statistical Package for Social Science version 5 (SPSS, Chicago, IL, USA) was used on an IBM-compatible personal computer.

Results

Study population

No significant differences in age, weight or height were found between the children with HSP and control subjects.

All HSP patients had palpable purpura of the lower extremities and buttocks, but in one child the skin rash also involved the trunk and upper extremities at onset. Abdominal pain occurred in six patients (40%). None of them required total parenteral nutrition. Eleven patients (73%) had joints involved (three arthritis and eight arthralgia) and five patients (33%) showed renal involvement, characterized by microscopical haematuria in four cases and gross haematuria in one case. This patient (number 2) had persistent microscopical haematuria with proteinuria (<300 mg \cdot 24 h⁻¹) and after 1 yr from presentation the patient underwent renal biopsy that showed focal mesangial proliferation with the deposition of immunoglobulin (Ig)A in the mesangial region. During the weeks preceding the purpura lesions, upper respiratory tract infections were reported in six cases (40%). At the time of hospital admission, throat cultures were positive for β -haemolytic streptococci in two patients. At laboratory examination platelet counts, serum complement (C3 and C4), and haemoglobin levels (12.91 \pm 1.01 g \cdot dL⁻¹) were normal in all patients. Serum IgA values were higher in six cases than the normal range for age [17]. The antistreptolysin O (ASO) titre was found to be high in four patients. Circulating immune complexes, ANA, RF and hepatitis B surface antigen were all negative.

In all but two (patient numbers 1 and 2) of the 15 children with HSP, clinical recovery was observed within 6 weeks from the onset of the disease.

Table 1. – Pulmonary function results of patients with Henoch–Schönlein purpura (HSP) studied at onset and compared with control subjects

	Patients with HSP		Control subjects	
	Actual	% Pred	Actual	% Pred
FEV1 L	1.61±0.52	98.8±2.5	1.73±0.39	100±1.3
FVC L	1.86±0.59	98.5±2.5	1.96±0.42	99.4±1.6
FEV1 %	86.6±5.47		87.2±4.88	
TLC L	2.32±0.72	98.4±1.6	2.43±0.57	99.1±1.6
RV L	0.50±0.25	98.6±5.4	0.46±0.21	97.6±6.0
$T_{L,CO_{ss}}$ mmol·min ⁻¹ ·kPa ⁻¹	3.32±0.81**	83.2±19.9**	4.10±0.79	101±18.5
$T_{L,CO_{sb}}$ mmol·min ⁻¹ ·kPa ⁻¹	3.75±1.16**	80.8±15.1**	5.22±0.93	94.9±10.1

Data are expressed as mean±sd. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; $T_{L,CO_{ss}}$, $T_{L,CO_{sb}}$: steady-state and single-breath transfer factor of the lung for carbon monoxide. **: p<0.01 versus controls.

Pulmonary function test results

The results of pulmonary function tests at the time of diagnosis are given in table 1. None of the 15 children with HSP had clinical signs of pulmonary disease or lung radiographic abnormalities during the acute phase of the disease, and none of them developed overt clinical lung involvement between the baseline and the second investigation. To assess differences between children with HSP and control subjects, after a logarithmic transformation of data with a non-normal distribution, an ANOVA was performed with the absolute mean values of the lung function test (FEV1, FVC, TLC, RV, $T_{L,CO_{ss}}$, and $T_{L,CO_{sb}}$), including sex as an independent variable and age, height and weight as covariates (table 1).

With the exception of $T_{L,CO}$, no significant differences between the affected and control individuals were found for any of the variables listed above. In fact, during the active phase of the disease only the corrected values of $T_{L,CO_{ss}}$ and $T_{L,CO_{sb}}$ were found to be significantly lower, both in absolute value (p=0.006 and p=0.004, respectively) and as a percentage of the expected values (p=0.007 and p=0.009, respectively) compared with controls (table 1).

There was no significant relationship between pulmonary function tests with symptoms and signs at onset, nor was there any correlation between variables and serum IgA concentration.

Follow-up evaluation

For technical reasons transfer factor measurement was obtained at the second evaluation only by the single-breath method. Table 2 shows the individual values of pulmonary function test expressed as a percentage of the predicted value for each child with HSP at baseline and at the second evaluation.

Although the mean value of $T_{L,CO_{sb}}$ improved from baseline (82±11% pred) to the second investigation (92±13% pred) this did not reach statistical significance (p=0.07) (table 2).

In all but two patients, clinical recovery was observed within 6 weeks from the onset of the disease. In one of these two patients (patient number 1) relapses of purpuric skin lesions occurred during the first 3 months of follow-up. The $T_{L,CO_{sb}}$ was 77% pred at onset and 73% pred after 43 months. The other patient (number 2) had recurrences of purpuric skin lesions during the next 12 months and persistent microscopical haematuria at the second evaluation. The $T_{L,CO_{sb}}$ was 104% pred at onset and 82% pred value at the second investigation (18 months after baseline evaluation). In the remaining eight patients the mean $T_{L,CO_{sb}}$ improved significantly from baseline (80±10% pred) to the second investigation (95±12% pred) (p=0.02).

Table 2. – Pulmonary function data at baseline and second evaluation

Patient No.	FEV1		FVC		FEV1 %		RV		TLC		$T_{L,CO_{sb}}$	
	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
1	94	98	97	97	73	94	107	98	99	98	77	73
2	101	102	101	104	84	73	99	80	101	101	104	82
3	99	101	99	100	85	91	92	88	97	98	77	114
4	99	100	98	99	87	92	94	106	98	100	83	83
5	101	101	100	100	89	92	95	90	99	98	86	91
6	101	102	100	101	90	91	102	104	100	103	76	110
7	99	99	97	98	93	96	104	103	98	99	90	96
8	100	101	100	101	82	85	102	103	100	101	94	100
9	93	97	91	96	97	96	105	104	97	99	61	85
10	101	100	101	99	85	95	94	83	98	101	77	82
Mean±sd	99±3	100±2	98±3	99±2	86±6	90±7	99±5	96±9	98±1	99±2	82±11	92±13

Results are expressed as percentage of predicted values (except for FEV1 %=FEV1/FVC ratio). 1st: baseline evaluation; 2nd: second evaluation. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; $T_{L,CO_{sb}}$: single-breath transfer factor of the lung for carbon monoxide.

Discussion

HSP is a diffuse necrotizing vasculitis affecting smaller vessels with the deposition of immune complexes containing IgA within vessels throughout the body and within the glomerular mesangial regions [18]. Clinically important pulmonary disease in HSP is extremely rare. A review of the literature reveals that respiratory complications have a high mortality rate, with only five out of nine paediatric patients surviving [7, 9].

In the present study 15 children with HSP free of clinical pulmonary symptoms and with normal chest radiographs were enrolled. The results clearly suggest a subclinical lung impairment assessed by pulmonary function test during the active phase of the disease. In particular, TL_{CO} measured by the steady-state and single-breath methods were both significantly reduced in children with HSP compared with the results obtained in the control group. In this series no correlation was found between the degree of $TL_{CO_{ss}}$ and $TL_{CO_{sb}}$ impairment, and the severity of the disease at onset. Although the mean value of TL_{CO} improved from baseline to the second investigation this did not reach statistical significance. The inability to detect a statistical difference at 5% confidence limits is probably due to the fact that two out of ten patients continued to show disease activity and deterioration of TL_{CO} . In one case (number 1) relapses of purpuric skin lesions were observed during the first 3 months of follow-up. The second case (number 2) had relapses of purpuric skin lesions during the 12 months following onset of the disease and microscopical haematuria persistent at the second evaluation. This patient underwent renal biopsy that showed focal mesangial proliferation with IgA mesangial deposition.

In spite of the high prevalence of lung function abnormalities, none of the patients developed overt clinical signs of lung involvement between the first and the second evaluation, suggesting that pulmonary function impairment alone should not be regarded as a sign of progressive lung disease.

Thus, the main finding of the present study was a reduced TL_{CO} that improved, with the exception of the two patients described above, at the second evaluation. However the precise significance of these changes is not clear. The pattern of pulmonary function observed may have been caused by interstitial lung processes. This might be explained by the presence of a diffuse vascular lung involvement related to the systemic nature of the inflammatory process. However, the impairment of the lung transfer factor is difficult to explain with the presence of pulmonary haemorrhage because where alveolar haemorrhage occurs the TL_{CO} tends to increase owing to the enhanced uptake of carbon monoxide by intra-alveolar haemoglobin.

There is only one study on pulmonary function in children with HSP [11]. CHAUSSAIN *et al.* [11] reported the presence of a low TL_{CO} in 96% of the patients in the absence of pulmonary symptoms, although radiological signs of interstitial lung involvement were present in 70% of the patients at the time of the investigations. In all cases normalization of TL_{CO} values was observed only after complete clinical recovery. In their work the authors suggested that the impairment of TL_{CO} may be related to alterations in the alveolar capillary membrane by IgA deposition during the active phase of the disease.

The lack of clinical and radiological signs did not ethically allow high-resolution computer tomography or bronchoscopic procedures (bronchoalveolar lavage, trans-bronchial lung biopsy) to be performed in these paediatric patients. However, pathological changes in the lung in patients with HSP have been observed in *post mortem* specimens and were characterized by necrosis of the capillary walls with septal and intra-alveolar haemorrhages [8, 10]. Immunochemistry studies showed granular deposition of IgA along the alveolar septa suggesting an immunopathogenetic mechanism in the development of the pulmonary lesion [8]. This histological feature of pulmonary capillaritis has also been reported in systemic vasculitides and particularly in systemic lupus erythematosus (SLE) [19]. It is well known that SLE is a connective tissue disease mediated by circulating immune complexes where the predominant reaction is leukocytoclastic vasculitis. Abnormalities of pulmonary function have been reported in children with SLE in the absence of clinical and radiographic pulmonary involvement [20, 21].

In conclusion, this study shows an early functional lung impairment in children with Henoch-Schönlein purpura without any clinical or radiological evidence of lung involvement, during the active phase of the disease. The follow-up data show that lung function impairment tends not to develop overt clinical signs. Further studies with a larger number of patients are needed to confirm these findings and to establish better the pathological lesions of sub-clinical lung involvement.

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