

Treatment of allergic alveolitis with methylprednisolone pulse therapy

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We report on a 13-year-old-boy who had been admitted to our hospital for dyspnea, hypoxia, and pulmonary infiltrates. The diagnosis of allergic alveolitis was based on history (provocation by exposure), lung function tests, bronchoalveolar lavage, and transbronchial lung biopsy. No specific allergen could be identified. Five courses of methylprednisolone pulse therapy (15 mg/kg on three consecutive days) stabilized the patient with normalization of lung function and blood gas analysis. Between pulses the boy returned to his home on a farm without relapse. It is estimated that the effect of a single pulse lasted for at least 2–4 weeks. We conclude that pulse therapy can be used instead of continuous therapy in this rare disease in childhood.

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Hypersensitivity pneumonitis (or allergic alveolitis) is a rare disease in childhood which is characterized by an insidious or hyper-acute onset of cough and respiratory crackles, hypoxia, infiltrates in chest X-ray and a restrictive pattern in pulmonary function tests. The etiology is considered to be a reaction to organic dust, but the pathogenesis is poorly understood. Histologically, it is characterized by: interstitial lymphocytic infiltration; non-caseating granulomas; and chronic fibrotic changes (1). Allergic alveolitis may cause diagnostic difficulties if no serologic response to antigens is found (2). The treatment usually consists of allergen avoidance and long-term systemic steroids. However, because of side-effects, non-compliance with therapy is not unusual. We report on a child where, in addition to allergen-avoidance measures, methylprednisolone pulse therapy (15 mg/kg over 3 days) without any continuous steroids was successful in treating symptoms and facilitating normalization of lung function and blood gas analysis, as well as preventing relapses.

Case report

The 13-year-old boy was admitted to the Department of Paediatric Cardiology of the German Heart Institute, Berlin, because of

cyanosis and dyspnea. He lived on a farm 100 miles north of Berlin where he had contact with various animals and organic dusts. He had been healthy until 6 weeks previously, when dyspnea first occurred upon exertion. The cardiologic examination revealed no abnormalities; however, his chest X-ray showed discrete bilateral opacifications and he was referred to our Department on the same day that the examination was performed. Physical examination disclosed visible cyanosis, tachypnea and inspiratory crackles. Body temperature was normal and, apart from a slightly elevated erythrocyte sedimentation rate (ESR), there were no signs of infection. Oxygen saturation SaO_2 was 85% and carbon dioxide tension (pCO_2) 35 mmHg in room air. In the pulmonary function laboratory 2 days later, his vital capacity (VC) was reduced to 40% predicted. It was not possible to perform carbon monoxide-diffusing capacity (DLCO). Diagnostic bronchoalveolar lavage (BAL) showed marked lymphocytosis with a CD4 : CD8 ratio of 0.6 and 5% CD57⁺ natural killer (NK) cells (Table 1; date: 07.05.97). No micro-organism was detected by polymerase chain reaction (PCR) amplification or upon culture. Serologic tests for virus, bacteria or markers of autoimmunity were negative. Leucocyte counts,

Table 1. Bronchoalveolar lavage (BAL) differential upon admission and after treatment

Date	Neutrophils	Macrophages	Lymphocytes	Eosinophils	CD57	CD4 : CD8
07.05.97	1.2	13.2	85.3	0.3	5%	0.6
26.06.97	1.0	18.0	80.5	0.5	13%	0.7
09.02.98	0.2	42	54.4	3.1	8%	0.9

The numbers of cells indicated are expressed as a percentage of the total number of cells recovered.

serum immunoglobulins, T-cell subsets in peripheral blood, antibodies to polysaccharide-encapsulated bacteria and serum lactate dehydrogenase (LDH) were within the normal range for age. Intradermal test with purified protein derivative (PPD) was negative.

Parallel to the administration of oxygen, antibiotic therapy with clarithromycin was started and the boy improved clinically within 2 days. The infiltrates on chest X-ray cleared and the boy was released home after 10 days with the provisional diagnosis of atypical pneumonia without a known pathogen. Oxygen saturation at rest was within the normal range while he was breathing room air, and his vital capacity (VC) had risen to 60% predicted (Fig. 1). A follow-up visit to a local pulmonologist was advised.

Five weeks later the boy was re-admitted to the hospital with dyspnea and hypoxia. His VC had decreased again to 40%. His SaO₂ upon light exertion was below 80% (Fig. 1, day 50). During the following weeks in hospital the boy improved without specific therapy, as demonstrated by the VC. The suspicion of hypersensitivity pneumonitis was raised for the first time. Another round of diagnostic workup was performed (Table 1). Thoracic computed tomography (CT) showed micronodular opacifications that were distributed throughout the lung fields but slightly more pronounced in the lung periphery. Results from one laboratory showed no precipitating immunoglobulin G (IgG) antibodies to various antigens, including aspergillus, while another laboratory found positive precipitating IgG antibodies in IgG enzyme-linked immunosorbent assay (ELISA) to the following antigens: pigeon, duck, and goose (questionable titer); *Aspergillus fumigatus* (low titer); and *A. versicolor* and *Penicillium brevicompactum* (intermediate titer). A repeat BAL showed lymphocytosis with a low normal-for-age CD4 : CD8 ratio and 13% NK cells (Table 1; date: 26.6.97). To exclude other diseases, a transbronchial biopsy was performed. The specimen revealed a non-caseating granuloma without necrosis. The patient was

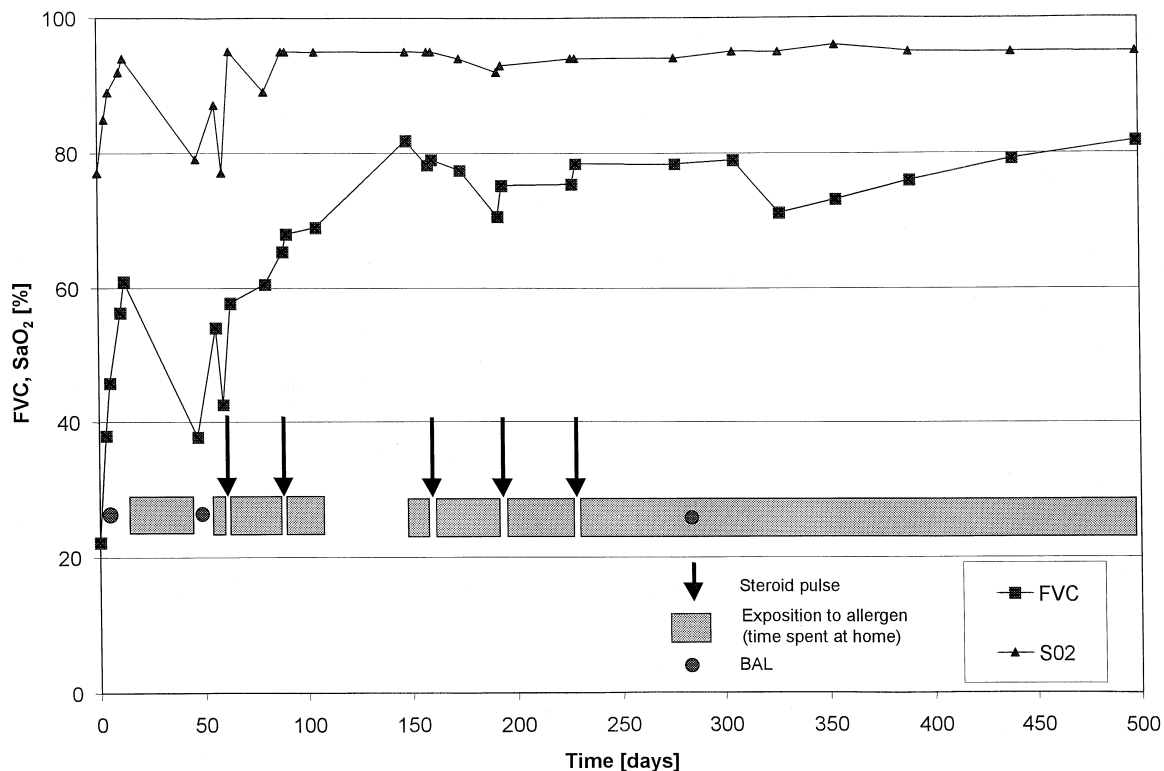


Fig. 1. Synopsis of the course of the parameters of SaO₂ upon exertion, vital capacity (VC) in relation to domestic antigen exposure of time spent at home (indicated by the solid horizontal bar), antigen avoidance and treatment of the patient.

sent home for 3 days over the weekend for a trial of re-exposure to antigens in his natural surroundings, and his VC and clinical condition deteriorated dramatically (Fig. 1, day 58). Traps for fungi at the boy's home revealed *aspergillus* in high proportions, although *aspergillus* titers had been low. From the clinical viewpoint, including the reproducible reactions in 'natural' provocation tests, the diagnosis of hypersensitivity pneumonitis was established. Laboratory tests (BAL, transbronchial biopsy, CT, pulmonary function testing and oxygen saturation upon exertion) were regarded as supportive, although there are limited data in childhood.

Therapy

The advantages and disadvantages of systemic continuous corticosteroid therapy vs. methylprednisolone pulse therapy were discussed with the parents and the patient. The parents had been informed that pulse therapy was not an established standard therapy in pediatric interstitial lung diseases and treatment failure could occur. Because of the paucity of side-effects in our experience with this treatment in more than 50 children with rheumatoid disease, the decision was made to institute pulse therapy. It was performed by administering 15 mg/kg methylprednisolone on three consecutive days. The boy's clinical condition improved dramatically after the first pulse on day 60, with SaO₂ upon exertion above 97% predicted and VC above 60%. The patient returned home immediately and his condition remained stable. When he returned to hospital 4 weeks later (day 90 in Fig. 1), his VC was 65% predicted, but SaO₂ upon exertion decreased to 90% predicted. A second pulse led to further recovery: his VC increased above 70% predicted. Most importantly, from that time point onwards he had no hypoxia, even upon exertion (Fig. 1).

In view of the dramatic initial clinical picture we felt that further avoidance measures were of central importance. We therefore persuaded the boy to take a holiday away from his home, in a summer camp for 6 weeks. During this time received no steroid pulses (day 110 to day 150 in Fig. 1). His VC increased to above 80% predicted. When he returned home, his VC deteriorated to 75% predicted (day 180 in Fig. 1), but after another three pulses it recovered and remained stable (last and fifth pulse at day 230 in Fig. 1). His VC showed deterioration only on day 320, without changes in oxygen saturation, and recovered spontaneously. Low-dose inhaled steroids (2 × 200 µg of

budesonide/day) were instituted as preventive long-term medication on day 270.

No systemic steroids were given between pulses. The boy has been stable since receiving pulse therapy. Nevertheless, and in contrast to this, the BAL after five pulses (and when the patient was in a clinically stable condition) still demonstrated lymphocytosis (Table 1; date: 9.2.98). In the CT scan on day 150, the alterations had improved. There were no side-effects of treatment; growth was completely normal (12 cm in 1 year). Measurements of bone density were not performed.

The relevance of exposure to material from a dump a few hundred meters away could not be proven. The temporary removal of the boy from his home was not possible, so he was advised to refrain from contact with animals. *Aspergillus* avoidance procedures included removal of plants from the indoor environment, new wallpaper, implementation of measures to dry out the apartment, and new floor seals.

The boy has been followed-up for a further 3 years without treatment; the disease has not recurred.

Discussion

This is, to our knowledge, the first published case of using methylprednisolone pulse therapy, successfully, to treat hypersensitivity pneumonitis in a child. Remarkably, the effect of a single pulse lasted several weeks, while avoidance measures were incomplete or impractical.

The diagnosis of hypersensitive pneumonitis in this patient was based on the following:

- the clinical picture with deterioration after exposure, which was reproducible three times, and improvement when the domestic milieu was avoided;
- results from BAL, as described typically for the disease in adults;
- histology of transbronchial biopsy; and
- imaging.

In our patient, two examinations for specific precipitating IgG antibodies were unable to confirm the diagnosis of hypersensitivity to a single or several avoidable antigens, and had only limited value (3).

The clinical diagnosis was characterized by impaired oxygen diffusion, best demonstrated by DLCO or deterioration of the SaO₂ upon exertion. The patient was asked to perform regular exercise tests (12-min walk) to enable detection of desaturations. In Fig. 1, it is shown how initial

VC and SaO₂ upon exertion increased and decreased in parallel. Subsequently, there was no decrease of SaO₂, and VC was the more sensitive parameter for sub-clinical deterioration. DLCO was not performed, however, so no direct comparison can be drawn.

The BAL results of our case are similar to those reported for adults. In the pediatric literature there are few reports on BAL lymphocyte subsets in hypersensitivity pneumonitis, possibly owing to the rarity of the disease. A report on BAL examinations from a large institution over a 1-year period did not include one single case of allergic alveolitis (4).

The most characteristic feature of this case is the clinical response to methylprednisolone pulse therapy. In the literature, the mainstay of therapy of hypersensitivity pneumonitis is allergen avoidance. If the antigen is not known, avoidance can only be attempted according to presumed exposure. This is considered impractical by many patients, however. The nature of the underlying hypersensitivity is unclear and the question is raised as to whether this is a temporary condition or if re-exposure will invariably lead to deterioration. Avoidance of exposure to the antigen is attempted, but not necessarily successful in healing allergic alveolitis.

The course of the disease can be downhill, resulting in permanent damage; symptomatic immunosuppression usually is the treatment of choice. As hypersensitivity pneumonitis results in type I and type III reactions, systemic corticosteroid treatment is used to prevent scarring and irreversible damage to the lung (5). The disadvantage is that the influence of antigen cannot be demonstrated. In addition, compliance with the corticosteroid doses applied is often poor because of side-effects, including cushingoid facies, hypertension, etc. The alternative is corticoid pulse therapy. We have previously applied this method of treatment successfully in a child with long-term steroid therapy and bronchiolitis obliterans organizing pneumonia (BOOP) after bone marrow transplantation (BMT) (6).

In most textbooks, corticosteroid pulse therapy in pulmonary medicine is advocated in children as a substitute when side-effects of continuous systemic treatment occur, but it is used increasingly as first-line treatment (7, 8). Unfortunately there are a lack of comparative studies. This case report gives insights into the pharmacodynamics and time course of action of methylprednisolone pulse therapy. It is shown in Fig. 1 that even domestic re-exposure to various antigens did not lead to a deterioration after one or two pulses. From experience with rheumatoid disease, the maximum

effect is achieved after 2 weeks. Recently, a series of case reports showed that pulse therapy was effective in interstitial lung diseases in children unresponsive to continuous systemic steroid therapy (9, 10). The efficacy was found to be superior to continuous systemic treatments in some reports. Dose-dependency has been described (11). In our case the patient did not show oxygen desaturation after the second pulse, although the VC decreased occasionally after exposure.

The clinical response to treatment is measured clinically (oxygen saturation upon exertion). The cell differential does not change within a short range and is often abnormal after prolonged treatment in interstitial lung disease of childhood and adulthood. It is remarkable that a marked BAL lymphocytosis can still be present, but there is no decrease of oxygen saturation. This finding is in agreement with sub-clinical alveolitis. The phenomenon has been described in sarcoidosis and cannot be taken as an indicator of detrimental disease activity.

In consequence, corticosteroid pulse therapy should be considered as an alternative first-line treatment in pediatric patients with hypersensitivity pneumonitis and included in prospective studies.

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