

# Paraneoplastic cerebellar degeneration preceding the diagnosis of Hodgkin's lymphoma

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## ABSTRACT

Paraneoplastic cerebellar degeneration (PCD) can present as a severe and (sub)acute cerebellar syndrome. PCD can accompany different kinds of neoplasms including small cell lung cancer, adenocarcinoma of the breast and ovary, and Hodgkin's lymphoma. A 34-year-old patient is described with acute dysarthria, gait ataxia and diplopia. Despite extensive laboratory and radiological evaluations in this patient with rapidly deteriorating cerebellar syndrome, the diagnosis of a paraneoplastic syndrome was only made after several months, when an anti-Tr antibody was detected in his serum. The search for Hodgkin's disease as concomitant disorder was then started and resulted in stage IIB disease. The patient was successively treated with six courses of etoposide, bleomycin, vinblastine and dexamethasone and radiotherapy, which resulted in a complete remission of the Hodgkin's disease. After starting therapy the cerebellar degeneration stabilised.

The pathogenesis of neuronal damage in central nervous system paraneoplastic disorders such as the one we describe is not completely understood. Antitumour therapy is assumed to be the important cornerstone in stabilising the neurological condition. Improvement of the cerebellar syndrome in anti-Tr autoantibody paraneoplastic disease is a rare achievement. Early recognition of the concomitant disorders (anti-Tr autoantibody disease and Hodgkin's lymphoma) is of crucial importance.

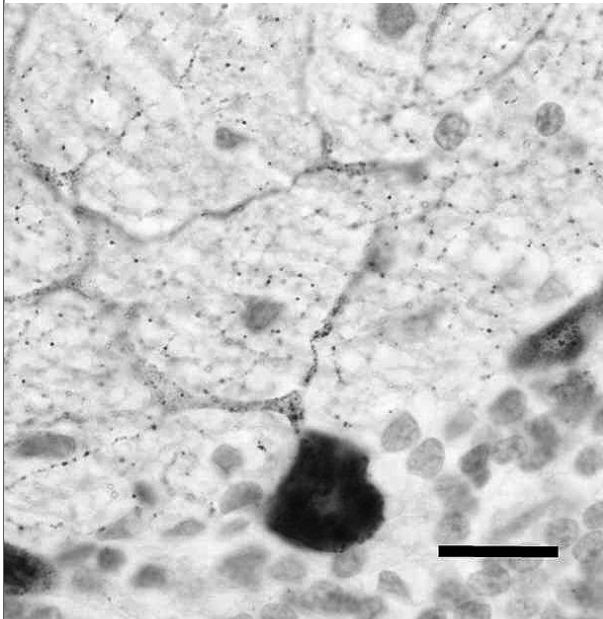
## KEY WORDS

Anti-Tr, cerebellar degeneration, Hodgkin's lymphoma, paraneoplastic

## INTRODUCTION

Paraneoplastic cerebellar degeneration (PCD) typically presents with (sub)acute, severe cerebellar ataxia.<sup>1</sup> PCD is most commonly associated with small cell lung cancer (SCLC), adenocarcinoma of the breast and ovary, followed by Hodgkin's lymphoma.<sup>2</sup> Sometimes the diagnosis of a malignant disease is made before the syndrome occurs. Usually, however, PCD precedes the underlying neoplastic disease, posing a diagnostic challenge. The detection of antineuronal autoantibodies directed against onconeural antigens helps diagnose the neurological syndrome as paraneoplastic and directs the search for an underlying tumour.<sup>3,5</sup> The autoantibodies associated with PCD include anti-Hu (SCLC), anti-Yo (breast and ovarian cancer) and anti-Tr (Hodgkin's disease). In 1976, Trotter *et al.* described an autoantibody in the serum of a patient with Hodgkin's lymphoma directed against cerebellar Purkinje cells and held the antibody responsible for the paraneoplastic symptoms.<sup>6</sup> Other reports followed, but it was not until 1997 that Graus *et al.* found an anti-Purkinje cell antibody in five Hodgkin's patients with PCD showing a characteristic immunoreactivity in the molecular layer of the cerebellum (*figure 1*). The antibody was named anti-Tr after the first two letters of Dr Trotter's name.<sup>7-9</sup> Recently, Bernal *et al.* analysed a series of 28 patients with PCD and anti-Tr antibodies. Of the 28 patients with anti-Tr immunoreactivity, 25 patients suffered from Hodgkin's disease while three had no demonstrable tumour.<sup>1</sup> Here we describe a patient presenting with an acute cerebellar syndrome leading to the diagnosis of Hodgkin's lymphoma several months later.

**Figure 1.** Paraffin sections of rat cerebellum incubated with biotinylated immunoglobulin G from an anti-Tr positive serum, counterstained with haematoxylin



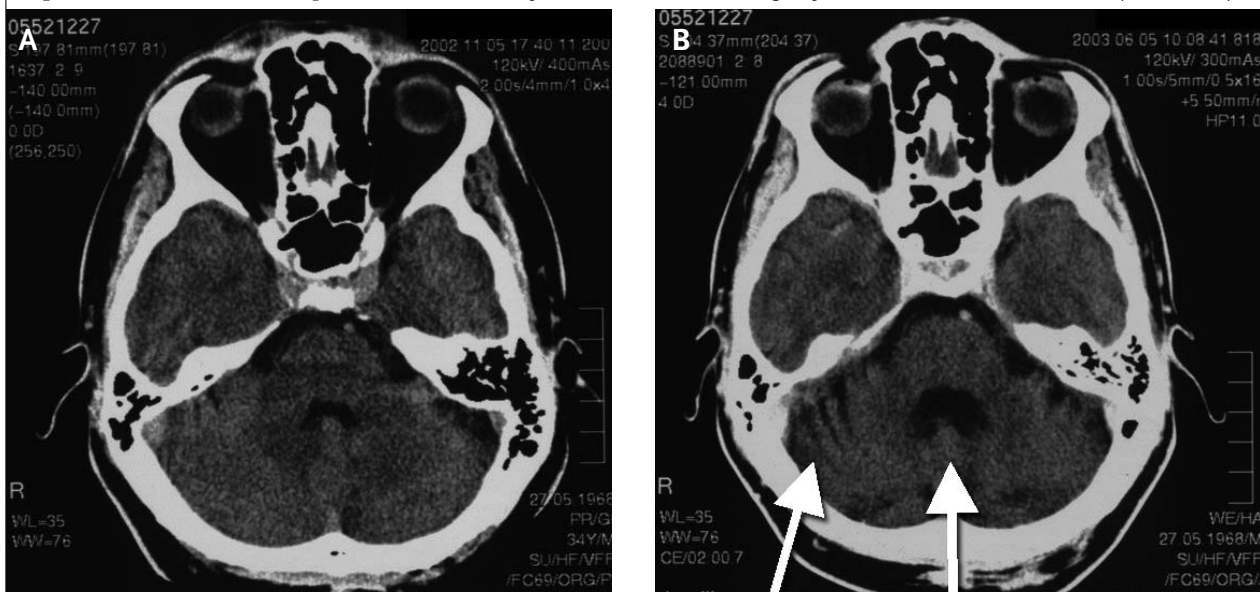
The typical anti-Tr pattern with punctate reactivity of the molecular layer and staining of the cytoplasm and proximal dendrites of Purkinje cells is shown.

## CASE REPORT

A 34-year-old male was admitted to the neurology ward because of acute dysarthria, gait ataxia and diplopia. He complained of headache accompanied by nausea and vertigo. There was no fever or any other systemic symptom at the time of presentation. Several months before admission, his family doctor had started him on paroxetine (30 mg daily) for depression. He smoked 20 cigarettes daily and had four to six alcoholic drinks during the weekend. Physical examination showed a slightly apathetic man without signs of meningeal irritation. He had normal blood pressure (135/85 mmHg), pulse (90 beats/min) and temperature of (37.5°C). His speech was dysarthric and there was a third-grade nystagmus to the left. No cranial nerve dysfunction or visual disturbances were noticed. Sensory examination and strength were normal. The finger-nose and heel-shin test were severely ataxic and the patient was incapable of walking without help, due to an unsteady and wide-based ataxic gait. Laboratory tests showed no signs of infection, and the erythrocyte sedimentation rate was 13 mm (in the first hour). Renal function, liver enzymes, glucose, alcohol level, serological tests (Lues, HIV, Lyme's disease, herpes viruses, ANF), vitamin E level, angiotensin-converting enzyme and tumour marker tests did not reveal the cause of the symptoms. Cerebral CT scan (figure 2A) and MR

scan (before and after administration of gadolinium contrast medium) were normal. Cerebrospinal fluid examination revealed pleiocytosis with lymphocyte counts of 462/3, glucose 3.47 mmol/l and total protein of 0.73 g/l. Furthermore a monoclonal IgG was present which was not found in the serum (IgG index 0.74). Microbiological examination of the cerebrospinal fluid (CSF) remained negative. Immunophenotyping of blood and CSF showed no monoclonal cell population. In the blood 16% of all mononuclear cells were B-cells and of all T cells, 43% showed CD4 expression, 26% CD8 expression. There was no increase in NK-cells. In the CSF 24% of all cells were B-lymphocytes and T-cell distribution CD4/CD8 cells equalled 3:1. CT scanning of the body did not show any malignancies, including lymphoma. A descriptive diagnosis of 'lymphocytic meningitis' was made but the cause of the severe cerebellar syndrome remained unclear. During the admission, the nystagmus disappeared spontaneously and the patient was discharged to a rehabilitation clinic. Some weeks later, the results of serum paraneoplastic antibody test, showed the presence of anti-Tr antibodies (titre 1:800), almost pathognomonic for Hodgkin's lymphoma. Physical examination showed a pathological lymph node in the right axilla. However, in the operating room, one week later, the lymph node had disappeared. Ultrasound examination also ruled out any axillary lymph node enlargement. FDG-PET scanning, again ten days later, showed increased FGD uptake in the right axilla and the neck (figure 3). Meanwhile, the patient was treated with plasmapheresis in an attempt to alleviate the cerebellar syndrome by decreasing the autoantibody titre. During the plasmapheresis his clinical condition stabilised. An axillary lymph node became palpable again and biopsy demonstrated a Hodgkin's lymphoma, nodular sclerosing type. Ann Arbor staging revealed stage IIB, weight loss occurred within several weeks as well as itching. At the start of his first chemotherapy cycle, i.e. etoposide, bleomycin, vinblastine and prednisone (EBVP), the antibody titre had risen to 1:3200. After two cycles of chemotherapy the titre had decreased to 1:800. The lymph nodes also decreased rapidly and were not palpable after two cycles. After the sixth cycle of EBVP the anti-Tr antibody was no longer detectable (figure 4). CT scan of the body showed complete remission after chemotherapy and involved field radiotherapy. The cerebellar syndrome had stabilised, but the patient still was incapable of walking without help and spoke in a dysarthric manner. No neurotoxic effects of vinblastine were observed. This was carefully examined, as it is a reported side effect of this cytostatic drug. CT scan of the brain six months after the first symptoms showed marked degeneration of gyri and widening of sulci of the cerebellum, indicating that supra- and infratentorial (cerebellar) tissue loss had occurred (figure 2B).

**Figure 2.** CT scan of the cerebrum of the patient described at diagnosis (A) and showing widening of the supratentorial ventricular system and the sulci of the cerebellum as a sign of tissue loss six months later (B; arrows)



**Figure 3.**  $^{18}$ Fluorodeoxyglucose positron emission tomography of the patient described

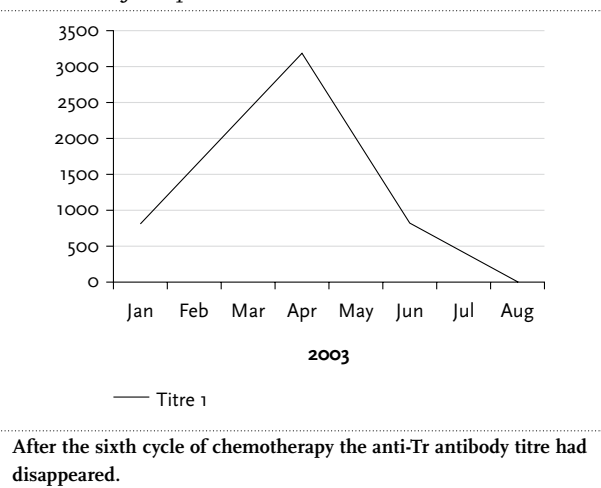


FDG uptake is striking in the neck and right axilla as a sign of localisation of the malignant disease. Uptake of FDG in the urinary bladder is considered physiological.

## DISCUSSION

With small cell lung, breast and ovarian cancer, Hodgkin's lymphoma belongs to the malignancies most often associated with PCD.<sup>2,3</sup> The possible association between Hodgkin's disease and cerebellar degeneration was noted some years ago.<sup>4,5</sup> Although the pathogenesis of PCD is

**Figure 4.** Concentration of anti-Tr antibody measured in serum of the patient described



still not understood, the presence of high titre antibodies directed against antigens in cerebellar Purkinje cells, the intrathecal synthesis of these antibodies and the presence of inflammatory infiltrates in the cerebellum strongly point to an autoimmune process. Anti-Tr antibody was named after John L. Trotter, who described a 21-year-old female with stage I Hodgkin's disease and cerebellar ataxia.<sup>6,7</sup> Serum of the patient showed strong immunofluorescent staining of cerebellar Purkinje cells on sections of normal human cerebellar tissue.<sup>6</sup> Anti-Tr is identified by its immunohistochemical staining pattern in fixed frozen cerebellar sections. The antigen reacting with the antibody has not yet been identified. Anti-Tr is clearly associated with both PCD and Hodgkin's disease.<sup>1,3,7-10</sup> The antibody

can be detected in serum as well as in cerebrospinal fluid thus for screening purposes the testing of serum suffices. The CSF of our patient was not tested for paraneoplastic antibodies.

The largest series of patients with anti-Tr associated PCD was recently published.<sup>1</sup> In the majority of these 28 patients the diagnosis of PCD was made prior to the Hodgkin's lymphoma diagnosis, as was the case in our patient. Others, however, describe a reverse sequence of events in the majority of patients with Hodgkin's lymphoma associated PCD.<sup>8</sup> The majority of patients with PCD and Hodgkin's lymphoma are of the male sex, in both series up to 80%.<sup>1,8</sup> Although Hodgkin's disease is about twice as common in men than in women the reason for this discrepancy is not known.

The prognosis of PCD associated with Hodgkin's lymphoma seems to be very poor. Of 28 patients described by Bernal *et al.* 86% suffered irreversible damage to the cerebellum.<sup>1</sup> The patients who recovered from their symptoms were all relatively young, under 40 years (as is the case in our patient). No relation to type or stage of the Hodgkin's disease is known. There is also no evidence that a decrease of the antibody titre by means of treating the underlying Hodgkin's disease predicts better outcome. If treatment of the underlying neoplasm is successful, the antibody disappears in most cases.<sup>1</sup> In general, early recognition and intensive treatment of the underlying malignancy is advocated in most paraneoplastic neurological conditions. As in our patient, the neurological disorder develops rapidly and neurons are quickly disturbed. By the time the diagnosis was made and treatment undertaken, the neurons had probably been destroyed and no sign of regeneration was obvious. As the CT scan after six months showed, the cerebellar tissue had partially disappeared despite lowering of the antibody titre.

Treatment options other than treating the underlying malignancy to lower antibody titres in paraneoplastic neurological disease have been described mainly in anti-Hu and anti-Yo antibody related syndromes. Anti-Yo antibodies are found in women with ovarian or breast cancer. Anti-Hu antibodies coexist with SCLC. Therapeutic interventions consist of intravenous administration of immunoglobulins, plasmapheresis (also applied to our patient) and immunosuppressive medication (prednisone, cyclophosphamide).<sup>11-17</sup> One of four patients with anti-neuronal antibodies described by Blaes *et al.* suffered from cerebellar degeneration as a result of anti-Yo antibodies and showed improvement of clinical condition after plasmapheresis followed by high-dose immunoglobulines.<sup>11</sup> Graus *et al.* described several series of patients with anti-Hu and anti-Yo (paraneoplastic) antibodies and neurological syndromes.<sup>12,13</sup> The mean duration of the neurological syndrome was 3.3 months at the onset of plasmapheresis. Antibody titres in serum of all patients decreased to 10 to 20% of the initial levels with plasmapheresis alone

or combined with prednisone or cyclophosphamide. No patients improved, some remained stable for at least six months if they also received treatment of the malignancy. In our patient the pre- and post-plasmapheresis antibody titres were not measured. Clinically he showed no improvement with two weeks of plasmapheresis, three times a week.

As noted before, the pathogenesis of neuronal damage in central nervous system paraneoplastic disorders is related to an autoimmune process. The hypothesis is that antigens normally expressed in the central nervous system are no longer restricted to this area, but are aberrantly (mutated or not) expressed in malignant tissue. This idea seems to hold true in case of, for example, PCD and anti-Hu or anti-Yo antibodies. The Hu- and Yo-antigens were identified as proteins normally expressed in neuronal cells and respectively SCLC and gynaecological- or breast tumour cells.<sup>16</sup> Tr-immunoreactivity however was discovered only in one out of 15 analysed samples of Hodgkin's lymphoma tissue of patients with PCD, anti-Tr antibodies and Hodgkin's lymphoma.<sup>1</sup> The biopsy specimen from the pathological lymphnode of our patient was not appropriately conserved to perform this test of Tr-immunoreactivity.

Bernal *et al.* also hypothesise that the character and origin of the immune process in PCD with Hodgkin's lymphoma may be different from paraneoplastic neurological syndromes in solid malignancies.<sup>1</sup> A polyclonal B-cell activation as described in patients with Hodgkin's lymphoma could be responsible for an autoimmune process in the cerebellum without a particular 'Tr antigen' being expressed by the malignant cells. It is also postulated that paraneoplastic disorders of the central nervous system can be the result of T-cell mediated cytotoxic response, antineuronal antibodies cause additional pathogenic effects.<sup>17</sup>

Whether lymphoma (progression) or the central nervous system condition will be the major prognostic factor in our patient is left for the future to decide.

## CONCLUSION

PCD presents with (sub)acute, severe cerebellar ataxia and should lead to prompt extensive diagnostic work-up. Positron emission tomography can, as also shown in our patient, be helpful localising an underlying tumour when antineuronal antibodies are identified.<sup>18</sup> Treatment of the underlying disease, in this case Hodgkin's lymphoma, could then be initiated as soon as possible, before irreversible cerebellar damage has occurred. Improvement of paraneoplastic central nervous system disorders is a rare achievement., therefore the central nervous system condition can be a considerable prognostic factor in PCD.

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