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Early-onset immunotherapy by intravenous immunoglobulin and corticosteroids in well characterized onconeural-antibody-positive paraneoplastic neurological syndrome

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Paraneoplastic neurological syndromes (PNS) are defined as immune mediated disorders, potentially affecting the whole nervous system, and are often associated with cancer [1]. Some clinical patterns are highly frequent in these syndromes, such as paraneoplastic cerebellar degeneration (PCD), limbic encephalitis (LE), subacute sensory neuronopathy (SSN) and Lambert–Eaton myasthenic syndrome (LEMS) [1]. In the 1980s, antibodies targeting intracellular neuronal proteins were described as biomarkers of PNS [1], advocating an underlying tumour. Indeed, more than 90% of patients with such antibodies suffered from an associated cancer. Recently, patients with a similar clinical presentation to PNS have been reported with other autoantibodies targeting cell-surface synaptic antigens. An associated cancer is less frequent in these patients. These findings have changed the concept of PNS [2], and the new PNS classification is now based on the location of the targeted antigen, instead of being defined by clinical symptoms or oncological status.

Two main groups of patients can be delineated according to the neuronal localization of the antigens targeted by the associated autoantibodies: group 1, antibodies with cytoplasmic neuronal antigens (CNA-antibodies); and group 2, antibodies with cell-surface neuronal antigens (CSNA-antibodies). Each group shows profound differences in the pathophysiology and the pathogenic role of the antibodies. Presence or absence of a tumour, prognostic and treatment responses also differ fundamentally from one group to the other [2]. In group 1 a tumour is almost always present, the neurological symptoms are severe and patients generally do not improve with immunomodulatory treatment. In contrast, in group 2 a tumour is rarely present, although some differences may be observed according to the subtype of associated antibody; the neurological symptoms are severe, but improve with immunomodulatory treatment in the majority of patients.

Patients with CNA-antibodies and PNS are rare, representing fewer than 0·01% of patients with cancer [3]. The main CNA-antibodies are directed against HuD [4], Ri [5], Yo [6], Ma1/2 [7], CV2/CRMP5 [8], Sox1 [9] and Zic4 proteins [10], and are associated strongly with tumours. Anti-Hu and anti-Yo antibodies are the most frequent [11], and are related strongly to small cell lung carcinoma (SCLC) [4] and gynaecological tumours (breast and ovarian carcinomas) [6], respectively. The pathophysiological role of CNA-antibodies is still under debate. These antibodies are not considered to be directly pathogenic, acting instead as markers of a cytotoxic T cell immune response directed towards neurones. Indeed, cerebral biopsies and autopsies of patients with these autoantibodies have shown the presence of cytotoxic T cells in parenchyma, associated with a profound loss of neurones [12]. Thus far, no animal models of PNS have successfully recreated the neuronal loss observed in patients, despite several attempts in murine models, including injection of anti-Hu and anti-Yo antibodies [13,14], immunization with purified Yo or HuD antigens [13,14] and injection with activated T cells (especially in the case of anti-Hu and anti-Yo antibodies) [14].

Irreversible neuronal death has been associated with the neurological symptoms presented by patients explaining the poor response to therapy. Given these therapeutic challenges, the main objective has been to stabilize the neurological symptoms. The relative rarity of these disorders, together with the heterogeneity of clinical patterns, are the main reasons explaining the scarce clinical trials in the field of PNS associated with CNA-antibodies. However, a few retrospective clinical studies [3–6,15–19] and prospective studies [20,21] (Table 1) exist and give some therapeutic guidance into the management of these conditions. The cornerstone in treating PNS associated with CNA-antibodies is curing the tumour. Tumour treatment must be the first objective to stop the immune reaction and the neuronal death. All retrospective studies suggest that rapid tumour treatment improves patient outcome. However, prospective studies are necessary to confirm

Table 1. Main treatment studies in group 1 antibodies: antibodies with cytoplasmic neuronal antigens (CNA-antibodies).

Antibodies (number of patients)	Type of study	Treatment modalities	Results	Authors
Hu, Yo, CV2 (329)	Retrospective	Corticoids, IVIg, PE, cyclophosphamide, azathioprine	Infrequent clinical improvement	Uchuya *et al.*, 1996 [19] Keime-Guibert *et al.*, 2000 [16] Rojas *et al.*, 2000 [6] Graus *et al.*, 2001 [15] Sillevis Smitt *et al.*, 2002 [18]
Yo, Hu, DNER and Ri (48)	Retrospective	Tumour treatment, immunosuppression	Few patients improved after tumour therapy	Shams'ili *et al.*, 2003 [5]
Ma2 (38)	Retrospective	Tumour therapy if applicable, and corticoids or IVIg	A third of patients with favourable outcome and 50% with clinical degradation	Dalmau *et al.*, 2004 [7]
Hu and Yo (9)	Retrospective	Rituximab	4/9 with clinical improvement	Shams'ili *et al.*, 2006 [17]
Hu, Yo and CV2 (26)	Retrospective	Tacrolimus	Few clinical improvement	Orange *et al.*, 2012 [3]
Hu, Yo, CV2 (20)	Prospective	PE and cyclophosphamide *versus* PE and chemotherapy	Better outcome in patients treated with cyclophosphamide	Vernino *et al.*, 2004 [21]
Hu (15)	Prospective	hCG	A third of patients harboured a significant improvement	van Broekhoven *et al.*, 2010 [20]

hCG = human chorionic gonadotrophin; IVIg = intravenous immunoglobulin; PE = plasma exchange.

these observations. The reported response to immunotherapy is generally poor, due probably to neuronal loss and death. Only two prospective trials have been conducted [20,21] in patients with anti-Hu, anti-Yo or anti-CV2/CRMP5 antibodies. One prospective open-label study compared plasma exchange plus conventional cancer chemotherapy (10 patients) to plasma exchange plus continuous oral cyclophosphamide (10 patients). Patients treated with cyclophosphamide showed sustained neurological improvement which continued after completion of the study [21]. A second prospective, uncontrolled, unblinded trial suggested a possible benefit of human chorionic gonadotrophin (hCG) in the treatment of PNS [20]. In the absence of large clinical trials, most therapeutic alternatives in patients with CNA-antibodies derive from observational clinical studies and case reports [3,5,15–19]. The usefulness of corticoids has been suggested in patients with anti-Hu [22], anti-Yo [23] antibodies or in patients with PNS and without antibodies [24,25]. Therapeutic effects of intravenous immunoglobulins (IVIg) appear to be limited, but in a very small proportion of patients with definite PNS (mainly with anti-Hu or anti-Yo antibodies) a favourable response has been described after IVIg therapy [26–28]. However, this response was not reproduced in a study of 19 patients with anti-Yo antibodies and cerebellar ataxia treated with immunomodulators (including IVIg) [5]. Plasma exchange is sometimes proposed instead of IVIg [29], and other authors have observed a stabilization of patients with anti-Hu and anti-Yo antibodies following treatment with cyclophosphamide in combination with corticoids and IVIg [16]. Stabilization of a few patients presenting anti-Hu and anti-Yo antibodies has been observed in uncontrolled and unblinded trials with rituximab [17,30,31]. Additionally, in a single-centre trial testing tacrolimus in PNS patients presenting with anti-Hu antibodies, some patients showed good tolerance and a trend towards neurological improvement [3]. Given the potential role of IVIg in the management of PNS patients, we are currently conducting a Phase II multicentre clinical trial to determine the efficacy of IVIg in the first 3 months of treatment. The trial (called Iason) is aiming to recruit 19 patients with anti-Hu, anti-Yo or anti-CV2/CRMP5 antibodies, and results are expected in 2016.

Further prospective clinical trials are essential to compare standardized treatment approaches more effectively, as well as to confirm that the improved outcomes observed in patients treated with immunomodulation are not the result of possible biases such as subtle differences in disease severity or differences in follow-up between retrospectively identified groups. These prospective trials must be conducted in homogeneous groups of patients according to the associated circulating autoantibodies in order to create guidelines for effective treatment.

Disclosure

J. H. has no conflicts of interest to disclose.

References

1 Graus F, Delattre JY, Antoine JC *et al*. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 2004; **75**:1135–40.

2 Lancaster E, Dalmau J. Neuronal autoantigens – pathogenesis, associated disorders and antibody testing. Nat Rev Neurol 2012; **8**:380–90.

3 Orange D, Frank M, Tian S *et al*. Cellular immune suppression in paraneoplastic neurologic syndromes targeting intracellular antigens. Arch Neurol 2012; **69**:1132–40.

4 Dalmau J, Graus F, Rosenblum MK, Posner JB. Anti-Hu-associated paraneoplastic encephalomyelitis/sensory neuronopathy. A clinical study of 71 patients. Medicine (Baltimore) 1992; **71**:59–72.

5 Shams'ili S, Grefkens J, de Leeuw B *et al*. Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: analysis of 50 patients. Brain 2003; **126**:1409–18.

6 Rojas I, Graus F, Keime-Guibert F *et al*. Long-term clinical outcome of paraneoplastic cerebellar degeneration and anti-Yo antibodies. Neurology 2000; **55**:713–5.

7 Dalmau J, Graus F, Villarejo A *et al*. Clinical analysis of anti-Ma2-associated encephalitis. Brain 2004; **127**:1831–44.

8 Honnorat J, Cartalat-Carel S, Ricard D *et al*. Onco-neural antibodies and tumour type determine survival and neurological symptoms in paraneoplastic neurological syndromes with Hu or CV2/CRMP5 antibodies. J Neurol Neurosurg Psychiatry 2009; **80**:412–6.

9 Titulaer MJ, Klooster R, Potman M *et al*. Antibodies in small-cell lung cancer and Lambert–Eaton myasthenic syndrome: frequency and relation with survival. J Clin Oncol 2009; **27**:4260–7.

10 Bataller L, Wade DF, Graus F, Stacey HD, Rosenfeld MR, Dalmau J. Antibodies to Zic4 in paraneoplastic neurologic disorders and small-cell lung cancer. Neurology 2004; **62**:778–82.

11 Giometto B, Grisold W, Vitaliani R *et al*. Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. Arch Neurol 2010; **67**:330–5.

12 Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. N Engl J Med 2003; **349**:1543–54.

13 Sillevis Smitt PA, Manley GT, Posner JB. Immunization with the paraneoplastic encephalomyelitis antigen HuD does not cause neurologic disease in mice. Neurology 1995; **45**:1873–8.

14 Tanaka K, Tanaka M, Igarashi S, Onodera O, Miyatake T, Tsuji S. Trial to establish an animal model of paraneoplastic cerebellar degeneration with anti-Yo antibody. 2. Passive transfer of murine mononuclear cells activated with recombinant Yo protein to paraneoplastic cerebellar degeneration lymphocytes in severe combined immunodeficiency mice. Clin Neurol Neurosurg 1995; **97**:101–5.

15 Graus F, Keime-Guibert F, Rene R *et al*. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain 2001; **124**:1138–48.

16 Keime-Guibert F, Graus F, Fleury A *et al*. Treatment of paraneoplastic neurological syndromes with antineuronal antibodies (anti-Hu, anti-Yo) with a combination of immunoglobulins, cyclophosphamide, and methylprednisolone. J Neurol Neurosurg Psychiatry 2000; **68**:479–82.

17 Shams'ili S, de Beukelaar J, Gratama JW *et al*. An uncontrolled trial of rituximab for antibody associated paraneoplastic neurological syndromes. J Neurol 2006; **253**:16–20.

18 Sillevis Smitt P, Grefkens J, de Leeuw B *et al*. Survival and outcome in 73 anti-Hu positive patients with paraneoplastic encephalomyelitis/sensory neuronopathy. J Neurol 2002; **249**:745–53.

19 Uchuya M, Graus F, Vega F, Rene R, Delattre JY. Intravenous immunoglobulin treatment in paraneoplastic neurological syndromes with antineuronal autoantibodies. J Neurol Neurosurg Psychiatry 1996; **60**:388–92.

20 van Broekhoven F, de Graaf MT, Bromberg JE *et al*. Human chorionic gonadotropin treatment of anti-Hu-associated paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 2010; **81**:1341–4.

21 Vernino S, O'Neill BP, Marks RS, O'Fallon JR, Kimmel DW. Immunomodulatory treatment trial for paraneoplastic neurological disorders. Neuro Oncol 2004; **6**:55–62.

22 Yamaguchi T, Kamiya K, Izumi N, Hisanaga T, Higashi K, Shima Y. Temporary improvement in activities of daily living after steroid therapy for the treatment of anti-Hu antibody-associated syndrome in a patient with advanced prostate cancer. J Pain Symptom Manage 2011; **41**:e6–8.

23 Thone J, Hohaus A, Lamprecht S, Bickel A, Erbguth F. Effective immunosuppressant therapy with cyclophosphamide and corticosteroids in paraneoplastic cerebellar degeneration. J Neurol Sci 2008; **272**:171–3.

24 Arjona A, Castellanos F, Graus F, Sanchez P, Escamilla C, Pascual ML. Steroid-dependent anti-Hu negative paraneoplastic encephalomyelitis and small cell lung carcinoma. J Neurol 1998; **245**:238–40.

25 Rajabally YA, Qaddoura B, Abbott RJ. Steroid-responsive paraneoplastic demyelinating neuropathy and myelopathy associated with breast carcinoma. J Clin Neuromuscul Dis 2008; **10**:65–9.

26 Phuphanich S, Brock C. Neurologic improvement after high-dose intravenous immunoglobulin therapy in patients with paraneoplastic cerebellar degeneration associated with anti-Purkinje cell antibody. J Neurooncol 2007; **81**:67–9.

27 Schessl J, Schuberth M, Reilich P *et al*. Long-term efficiency of intravenously administered immunoglobulin in anti-Yo syndrome with paraneoplastic cerebellar degeneration. J Neurol 2011; **258**:946–7.

28 Wiles CM, Brown P, Chapel H *et al*. Intravenous immunoglobulin in neurological disease: a specialist review. J Neurol Neurosurg Psychiatry 2002; **72**:440–8.

29 Meloni C, Iani C, Dominijanni S *et al*. A case report of plasma exchange therapy in non-paraneoplastic cerebellar ataxia associated with anti-Yo antibody. Ther Apher Dial 2004; **8**:500–2.

30 Coret F, Bosca I, Fratalia L, Perez-Griera J, Pascual A, Casanova B. Long-lasting remission after rituximab treatment in a case of anti-Hu-associated sensory neuronopathy and gastric pseudoobstruction. J Neurooncol 2009; **93**:421–3.

31 Esposito M, Penza P, Orefice G *et al*. Successful treatment of paraneoplastic cerebellar degeneration with Rituximab. J Neurooncol 2008; **86**:363–4.