

Treatment of Paraneoplastic Neurological Syndromes



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Paraneoplastic neurological syndromes (PNS) are rare complications of cancer that often herald the tumour diagnosis. Whereas some syndromes affect only certain parts of the nervous system, other syndromes involve both central and peripheral neurons, resulting in complex clinical manifestations.¹ The syndromes are believed to be immune-mediated, caused by T cell, B cell and macrophage responses to antigens present on tumour cells and on neurons and glia cells (Figure 1).² Activation of B cells results in the production of onconeural antibodies that are highly useful diagnostic markers for a paraneoplastic aetiology. According to diagnostic criteria, the presence of a well-characterized onconeural antibody in a patient with neurological symptoms defines the disease as paraneoplastic even in the absence of detectable malignancy.³ Onconeural antibodies are detected in about 60% of patients with PNS. PNS and onconeural antibodies have been discussed in a previous review in this journal.⁴

The symptoms as well as the severity of the PNS are heterogenous, depending on which parts of the peripheral and central nervous system are affected. Some syndromes have a high mortality rate, such as paraneoplastic

encephalomyelitis and brain stem encephalitis, whereas other syndromes are less lethal but leave the patients with disabling neurological deficits, such as paraneoplastic cerebellar degeneration and peripheral neuropathy. The rapidly progressive and often dramatic nature of the PNS symptoms requires urgent therapeutic considerations. Nevertheless, the rarity of PNS limits the number of published therapy studies, in particular studies with a prospective design. Thus, there is no class I or II evidence for PNS therapy except for the syndromes that affect the neuromuscular junction (paraneoplastic myasthenia gravis, Lambert-Eaton myasthenic syndrome, and neuromyotonia). Many patients receive concomitant anti-neoplastic therapy and immunotherapy, but so far there is no standard care for any of the PNS. This review focuses on the therapeutic options of PNS, but does not include the autoimmune neuromuscular diseases.

Anti-neoplastic therapy

The cornerstone of PNS therapy is resection of the tumour and/or oncological treatment, in order to eradicate the systemic antigenic source. Tumour removal is an independent predictor of

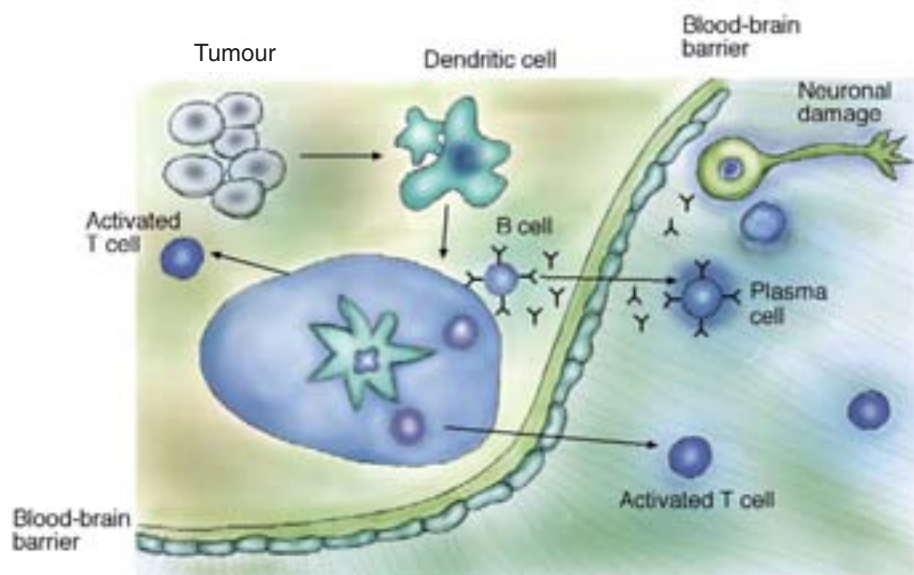


Figure 1: Plasma cells and cytotoxic T cells can cross the blood-brain-barrier and react with antigens shared by tumour cells and cells of the nervous system (onconeural antigens).

Table 1: Paraneoplastic neurological syndromes (PNS) and response to therapy

PNS	Tumour therapy	Immunotherapy	Symptomatic therapy
LE	Yes, especially when treated early	Variable. Patients with VGKC /NMDA antibodies respond best	Yes
SSN	Yes, especially when treated early	Rare	Yes
CD	Yes, especially in Hodgkin's	Rare	Yes
O-M	Yes	Often in children. Occasionally in adults.	Yes

LE: Limbic encephalitis; SSN: Subacute sensory neuropathy; CD: Cerebellar degeneration; O-M: Opsoclonus-myoelonus.

Early diagnosis of PNS is of great importance to obtain the best results of treatment. The cornerstone of PNS treatment is resection of the tumour and/or oncological treatment

improvement or stabilization in PNS patients.⁵ Thus, malignancy screening should be prompt and thorough in all patients with a suspected PNS. If conventional radiological examinations fail to detect cancer, a FDG-PET scan should be performed to increase the sensitivity for detection of small tumours or mediastinal lymphadenopathy.⁶ The sensitivity of FDG-PET is poorer in antibody-negative patients.

None of the onconeural antibodies are 100% organ-specific, but the identification of one of the well-characterized antibodies often indicates the most likely sites of malignancy. Exploratory surgery to diagnose occult malignancy may be considered in selected antibody-positive patients. For instance, orchiectomy in young males with Ma2-antibody associated encephalitis resulted in histological confirmation of cancer.⁷

In most cases, an aggressive diagnostic approach will result in cancer detection. If possible, histological verification of malignancy should be obtained, and expression of the relevant antigen should be confirmed to exclude the possibility of a second cancer. If complete malignancy screening, including whole-body FDG-PET is negative, we recommend immunotherapy and repeated investigations within 6 months.⁸

Immunotherapy

Given the immune-mediated pathogenesis of PNS, concomitant immunotherapy is administered to most patients. This includes plasmapheresis; iv IgG, corticosteroids, cyclophosphamide, tacrolimus and rituximab. The response to immunotherapy in PNS is highly variable, and patients with involvement of the peripheral nervous system usually respond

better compared to patients with manifestations from the central nervous system.⁹ This difference is largely due to the fact that paraneoplastic synaptic disorders of the peripheral nervous system are caused by antibodies that are pathogenic, e.g. paraneoplastic Lambert-Eaton syndrome, neuromyotonia and myasthenia gravis which are caused by VGCC, VGKC and AChR/Musk antibodies, respectively. The antigen targets of these antibodies are located in or in close proximity to the cell membrane. The immunotherapy regimens used in these disorders exert their main beneficial effects by lowering the amount of circulating antibodies, as well as suppressing the local immune response in the neuromuscular junction. Treatment of autoimmune neuromuscular diseases is reviewed elsewhere.¹⁰

PNS affecting the central nervous system are usually more or less refractory to treatment with immunotherapy. This can be explained by several factors, including the T cell dominated immune response, the blood-brain-barrier and the limited potential of regeneration of the central nervous system. Even if immunotherapy results in a decline in serum antibody titres, this is seldom associated with clinical improvement. Therefore, serial determination of antibodies cannot be used to monitor neurological outcome or tumour evolution in PNS.¹¹

Patients with paraneoplastic cerebellar degeneration associated with Yo or Hu antibodies are usually unresponsive to immunotherapy, although there are case reports of an apparent benefit of treatment with rituximab.¹² Such clinical responders have often had a short duration of neurological symptoms. Paraneoplastic opsoclonus-myoclonus is the only PNS that affects paediatric patients with associated neuroblastoma.

Whereas adult patients with paraneoplastic opsoclonus-myoclonus only occasionally benefit from immunotherapy, children may respond quite well to high-pulse dexamethasone and other immunosuppressive regimens.¹³

Among the PNS affecting the central nervous system, limbic encephalitis constitutes a heterogeneous group of disorders, of which some have a more favourable response to immunotherapy. As recently pointed out by Dalmau and Rosenfeld, limbic encephalitis should be classified into subphenotypes according to the location of the target antigens.¹ Limbic encephalitis associated with Hu, Ma2, CRMP5 or amphiphysin antibodies rarely respond to immunotherapy, although patients with testicular cancer and Ma2 antibodies seem to have a more favourable prognosis. On the other hand, patients with associated VGKC or NMDA antibodies benefit from immunotherapy.¹

In general, the effect of immunotherapy in PNS of the central nervous system seems to depend upon the severity as well as the duration of the neurological symptoms.¹⁴ Most PNS have a subacute onset and stabilization within the course of a few months. Even patients with PNS and a pronounced neuronal loss, as paraneoplastic cerebellar degeneration, have been shown to respond to immunotherapy when administered very early on in the disease.¹⁶ This indicates that an acute stage of inflammation precedes irreversible neuronal damage. Immunotherapy should therefore be administered concomitantly with anti-neoplastic therapy as early as possible. However, there are no absolute guidelines for the priority of the different immunotherapy regimens.

Symptomatic treatment

Many PNS patients have disabling neurological symptoms, and the need for supplementary symptomatic treatment should be evaluated in all patients. This includes physical therapy, speech therapy for patients with cerebellar or brain stem dysfunction; antidepressants, neuroleptics or antiepileptic medication for limbic encephalitis; analgesics, antidepressants or antiepileptic drugs for neuropathic pain, as well as supportive therapy. Autonomic dysfunction, which often occurs in patients with subacute sensory neuronopathy, should also be treated.⁸

Conclusions

Early diagnosis of PNS is of great importance to obtain the best results of treatment. The cornerstone of PNS therapy is resection of the tumour and/or oncological treatment. PNS are associated with various onconeural antibodies, and the response to concomitant immunotherapy depends on the location of the target antigens. PNS with onconeural antibodies against cell-surface antigens, in particular the neuromuscular diseases, usually respond to immunotherapy, whereas PNS with onconeural antibodies against intracellular antigens are usually refractory to such therapy. ♦

REFERENCES

- Dalmau J, Rosenfeld MR. *Paraneoplastic syndromes of the CNS*. *Lancet Neurol* 2008;7:327-40.
- Storstein A, Vedeler CA. *Paraneoplastic neurological syndromes and onconeural antibodies: clinical and immunological aspects*. *Adv Clin Chem*. 2007;44:143-85.
- Graus F, Delattre JY, Antoine JC, Dalmau J, Giometto B, Grisold W, Honnorat J, Smitt PS, Vedeler C, Verschuren JJ, Vincent A, Voltz R. *Recommended diagnostic criteria for paraneoplastic neurological syndromes*. *J Neurol Neurosurg Psychiatry*. 2004;75:1135-40.
- Vincent A, Bien C. *Paraneoplastic neurological diseases*. *ACNR* 2007;7:6-8.
- Keime-Guibert F, Graus F, Broët P, Reñé R, Molinuevo JL, Ascaso C, Delattre JY. *Clinical outcome of patients with anti-Hu-associated encephalomyelitis after treatment of the tumor*. *Neurology*. 1999;53:1719-23.
- Younes-Mhenni S, Janier MF, Cinotti L, Antoine JC, Tronc F, Cottin V, Ternamian PJ, Trouillas P, Honnorat J. *FDG-PET improves tumour detection in patients with paraneoplastic neurological syndromes*. *Brain*. 2004;127:2331-8.
- Mathews RM, Vandenbergh R, Garcia-Merino A et al. *Orchiectomy for suspected microscopic tumor in patients with anti-Ma2-associated encephalitis*. *Neurology* 2007;68:900-5.
- Vedeler CA, Antoine JC, Giometto B, Graus F, Grisold W, Hart IK, Honnorat J, Sillevs Smitt PA, Verschuren JJ, Voltz R. *Paraneoplastic Neurological Syndrome Euronetwork. Management of paraneoplastic neurological syndromes: report of an EFNS Task Force*. *Eur J Neurol*. 2006;13:682-90.
- Uchuya M, Graus F, Vega F, Rene R, Delattre JY. *Intravenous immunoglobulin treatment in paraneoplastic neurological syndromes with antineuronal autoantibodies*. *J Neurol Neurosurg Psych* 60:388-92.
- Skeie GO, Apostolski S, Evoli A, Gilhus NE, Hart IK, Harms L, Hilton-Jones D, Melms A, Verschuren J, Horge HW. *Guidelines for the treatment of autoimmune neuromuscular transmission disorders*. *Eur J Neurol* 2006;13:691-9.
- Lladó A, Mannucci P, Carpentier AF, Paris S, Blanco Y, Saiz A, Delattre JY, Graus F. *Value of Hu antibody determinations in the follow-up of paraneoplastic neurologic syndromes*. *Neurology*. 2004;63:1947-9.
- Shamsili S, de Beukelaar J, Gratama JW, Hooijkaas H, van den Bent M, van't Veer M, Sillevs Smitt P. *An uncontrolled trial of rituximab for antibody associated paraneoplastic neurological syndromes*. *J Neurol*. 2006;253:16-20.
- Ertle F, Behnisch W, Al Mulla NA, Bessiso M, Rating D, Mechttersheimer G, Hero B, Kulozik AE. *Treatment of neuroblastoma-related opsoclonus-myoclonus-ataxia syndrome with high-dose dexamethasone pulses*. *Pediatr Blood Cancer*. 2008;50:683-7.
- Blaes F, Strittmatter M, Merkelbach S, Jost V, Klotz M, Schimrigk K, Hamann GF. *Intravenous immunoglobulins in the therapy of paraneoplastic neurological disorders*. *J Neurol*. 1999;246:299-303.
- Widdess-Walsh P, Tavee JO, Schuele S, Stevens GH. *Response to intravenous immunoglobulin in anti-Yo-associated paraneoplastic cerebellar degeneration: case report and review of the literature*. *J Neurooncol* 2003;63:187-90.

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