Paraneoplastic cerebellar degeneration in olfactory neuroepithelioma

Anti-Hu antibody was first discovered in patients with paraneoplastic encephalomyelitis associated with small cell lung cancer (SCLC). This antibody recognizes proteins comprised in the Hu family expressed by neuronal cells as well as SC1 or SC2. After the first report, anti-Hu antibody was found in other neoplasms including prostate and breast cancer, adrenal carcinoma, chondromyxosarcoma, neuroblastoma, and neuroendocrine neoplasms at other sites. Olfactory neuroepithelioma (9523-3) is thought to differ from classic neuroblastoma (9500-3) in its expression pattern of tyrosine hydroxylase, MYCN amplification, and fusion of the Ewing sarcoma gene and the Friend leukaemia virus integration 1 gene or the ETS related gene.

Anti-Hu antibody in association with olfactory neuroepithelioma has not been reported previously. We report a patient with cerebellar ataxia that paralleled the recurrence of the tumour. Serum and cerebrospinal fluid (CSF) from the patient contained anti-Hu antibody (1:1920 and 1:64, respectively) (indirect immunofluorescence and Western blotting for recombinant HuD). Serum:CSF antibody titre ratio was 30. The ratio for CSF/serum antibody titre/(CSF/serum albumin) was 1.8. These values indicated that intrathecal synthesis of anti-Hu antibody had stopped at this time point. Other anti-neuronal antibodies including anti-Yo, Ri, CV2, Tr IA, amphiphysin, and glutamic acid decarboxylase were all negative. Systemic examination including 67Ga-citrate scintigraphy did not disclose malignant tumours. Immunohistochemistry with anti-HuD antibody (Santa Cruz, sc-9977, x100) revealed that a part of the tumour expressed Hu antigen (fig 1).

Over the course of 4 years after discharge, the cerebellar ataxia did not worsen further in the absence of immunological treatment. Follow up thoracic CT and tumour marker study did not disclose other malignant tumours. There was no evidence of the recurrence of olfactory neuroepithelioma.

CONCLUSION

This patient presented cerebellar ataxia of the trunk and lower limbs that progressed rapidly within approximately 6 months after the second surgery and stabilised thereafter. This clinical course is not inconsistent with the natural course of paraneoplastic cerebellar degeneration. Although isolated cerebellar ataxia in anti-Hu antibody positive patients is rare (4/200 patients), a high titre of serum anti-Hu antibody (1:1920) corroborated the diagnosis of paraneoplastic syndrome.

The expression of the HuD protein by the olfactory neuroepithelioma confirmed the diagnosis.

Olfactory neuroepithelioma is a neuroectodermal neoplasm that arises from the olfactory epithelium. It is distinguished from classic neuroblastoma as described by Sorensen et al. Unlike neuroblastoma, olfactory neuroepithelioma shows differentiation to the neural processes and glandular structure and is rarely associated with catecholamine secretion. In addition, olfactory neuroepithelioma expresses epithelial markers such as cytokeratin and a 34 kDa epithelial membrane glycoprotein recognised by monoclonal antibody named Ber-EP4. The tumour in this case expressed both Ber-EP4 and cytokeratin (see Okabe et al, case no. 6). Moreover, it also expressed luteinising hormone releasing hormone. The expression pattern of Ber-EP4 and cytokeratin was heterogeneous in this tumour. These findings suggest that the tumour in this case had arisen from the olfactory placode and was distinct from classic neuroblastoma arising from the neural crest. This neuroepithelial tumour has not been reported to be associated with paraneoplastic syndrome. Our data clearly demonstrate the expression of Hu antigen by the olfactory neuroepithelioma cells and the presence of Hu antibody in his serum and CSF. It is interesting that neurological manifestations developed in parallel with the recurrence of the tumour. The recurrence might have enhanced immune response. Despite resection of the recurrent tumour, the cerebellar ataxia worsened for several months after surgery. However, it did not progress thereafter. In patients with neurological symptoms and Hu antibody, olfactory neuroepithelioma should be considered when a neoplasm is not found at the common sites such as the lung or breast.

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Figure 1 Immunohistochemistry using anti-HuD antibody. A part of the patient’s tumour expressed HuD antigen (x400).

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www.jnnp.com
The collagen 1A2 polymorphism rs42524, which is associated with intracranial aneurysms, shows no association with spontaneous cervical artery dissection (sCAD)

In the last decade, extracranial spontaneous cervical artery dissection (sCAD) became increasingly recognised as a common cause of juvenile stroke. Hereditary connective tissue diseases such as Ehlers-Danlos syndrome type IV (EDS IV) and Marfan syndrome can be associated with sCAD and clinical signs of mild connective tissue weakness have been described in some patients with sCAD. Brandt and co-workers found connective tissue aberrations mainly affecting the collagen fibres in skin biopsies of patients with sCAD. Similar skin aberrations were found in patients with intracranial aneurysms (IA). A familial association of IA and sCAD has been observed in a few families. These findings suggest that connective tissue abnormalities are common to both diseases and might predispose to IA as well as to sCAD. Recently, association between the functional coding single nucleotide polymorphism (SNP) rs42524 in the collagen 1A2 (COL1A2) gene and IA has been described. The SNP rs42524 causes a base change G1645C and an amino acid change p.Val548Ile. The genotype and allele frequencies of the SNP rs42524 are shown in Table 1. Genotype frequencies in the patients, as well as in the control group, were in good agreement with Hardy-Weinberg equilibrium (p = 0.49 for controls and p = 0.47 for patients). Neither genotype nor allele frequencies showed significant differences between sCAD patients and controls in the whole sample, after stratification for the affected vessel (ICA or VA) (table 1) or after stratification for gender (results not shown).

Table 1 COL1A2 rs42524 genotypes

<table>
<thead>
<tr>
<th>Group</th>
<th>Genotypes</th>
<th>Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GG</td>
<td>CG</td>
</tr>
<tr>
<td>All sCAD</td>
<td>87 (61)</td>
<td>48 (33)</td>
</tr>
<tr>
<td>sCAD of ICA</td>
<td>57 (64)</td>
<td>28 (31)</td>
</tr>
<tr>
<td>sCAD of VA</td>
<td>27 (55)</td>
<td>17 (35)</td>
</tr>
<tr>
<td>Controls</td>
<td>98 (61)</td>
<td>54 (33)</td>
</tr>
</tbody>
</table>

Values are n (%), except for the p values. ICA, internal carotid artery; VA, vertebral artery. Six individuals suffered from concomitant sCAD of ICA and VA and were excluded from the subgroup analysis.

The collagen 1A2 gene is located on chromosome 7q22.1, a chromosomal region showing linkage with IA. The SNP rs42524 in the COL1A2 gene showed strong association with IA in a Japanese IA cohort and supposedly influences the thermal stability of collagen. We therefore investigated this SNP in sCAD patients because of the presumed pathophysiological similarities between both diseases. We did not find an association between sCAD and the SNP rs42524. However, it can not be excluded that this is due to ethnically determined differences in allele frequencies, because the chromosome 7q locus for IA as well as the association with the SNP rs42524 were originally found in a Japanese sample in which the C allele has a frequency of only 2.7% in the control group, while we studied a Caucasian population in which the C allele had a frequency of 23%. The sample size of the Japanese study (260 IA patients) and of our own study (144 sCAD) were too small to draw any conclusions with respect to the frequency of the C allele. In summary, this study renders it unlikely that the SNP rs42524 plays a major role in the pathogenesis of sCAD in Caucasians. However, this study does not exclude the possibility that other polymorphisms in the COL1A2 gene, which is a very large gene covering 37 000 bp of genomic DNA, are associated with sCAD.

The following websites have been mentioned in this letter: http://kursus.kvl.dk/shares/ventgen and http://statgen.iop.kcl.ac.uk/gpc/.

Electronic-database information

The the following websites have been mentioned in this letter: http://kursus.kvl.dk/shares/ventgen and http://statgen.iop.kcl.ac.uk/gpc/.

References

The recent major advances in the chronic form. The recent major advances in highly active anti-retroviral therapy (HAART) neurology of AIDS continues often in a more chronic form. The recent major advances in basic and clinical research are reflected in the extensive new information presented in the second edition of this comprehensive book.

The previous four sections have now been expanded to 12 sections divided into several chapters with multiple contributors, including clinicians, patients, and healthcare professionals.

The book starts with a panel discussion setting the scene of the subsequent text and emphasising the challenges for the future.

The first five sections cover advances in basic research on HIV including molecular and cellular biology, immunology, vaccines, the blood brain barrier, and animal models and mechanisms of neurotoxicity including host factors and cellular factors. Parallels are drawn with other neurodegenerative diseases. Section 6 is a poignant collection of patients’ accounts of living with neurological complications of AIDS. The next section deals comprehensively with the clinical aspects including dementia, more subtle cognitive disorders seen since the introduction of HAART, spinal cord disease, peripheral neuropathy, myopathy, neoplasms, opportunistic infection, and psychiatric disorders. A section on diagnostics follows including imaging and CSF markers. There is then an expanded paediatric section followed by discussion of antiretroviral and adjunctive drug treatment. The last section reviews the social and behavioural consequences of HIV infection including legal and ethical issues.

The book is very well illustrated throughout.

This outstanding book therefore provides an up to date comprehensive review of the basic science and the clinical aspects of the neurology of AIDS whilst emphasising future likely developments.

It is highly recommended for clinicians, research scientists, students, and other professionals involved in the care of these patients.

J Ball

Classification and diagnosis of headache disorders

This volume of Frontier’s in Headache Research focuses on the application in research and clinical practice of the International Classification of Headache Disorders II (2004).

Section I presents epidemiological considerations, general principles in headache classification, and use of tools such as questionnaires, structured interviews, diaries, and diagnostic software programmes. Section II presents the sub-classification of migraines with and without aura and chronic migraine, probably the most well supported by epidemiological and genetic evidence.

In section III fervent debate continues about the entity ‘Tension-type headache’ and nuances in classification—in frequent, frequent, and chronic tension-type headache. The diagnostic and pathophysiological basis for the core trigeminal autonomic cephalalgias (cluster headache, paroxysmal hemicrania, and SUNCT) is followed by syndromes that occupy the fringe of accepted sub-classifications—for example, hypnic headache, haemorrhagic continua, and new persistent daily headache. There is elaboration on a more pragmatic and practical ordering of other primary headache disorders such as idiopathic stabbing, cough, exertional, and sexual headache.

Sections IV and V provide the most interesting and thought provoking aspect of headache classification—the secondary headaches—undoubtedly the least evidence-based and consequently the most wanting in reclassification. The chapters discuss the literature and clinical characteristics of disorders such as post-traumatic headache, headache associated with substance (mediation) use, infection, and vascular disorders. The chapter “Cranial Neuropilas and Central Causes of Pain” is superbly written. It dispels the myths of ophthalmoplegic ‘migraine’, Eagle’s syndrome, and Vidian neuralgia (was it all cluster headache?), while clarifying the phenotype of neuralgia associated with single nerves and their branches—for example, supraorbital neuralgia.

Section VI elaborates upon the successes and difficulties of implementation of ICDH II in practice and research. As one author points out, if a classification is not user friendly, it won’t be used. Therefore, the call for a revised shortened classification for clinical practice, reserving the complexities of diagnostic hierarchy to the researcher, is required.

The preface concludes with, “Hopefully it (the current volume) will be useful and interesting reading for all those caring for headache patients as well as for researchers in headache, and others with a general interest in disease classification”. It adeptly delivers as intended. It is easy to read, informative, provides helpful tools for the practising clinician, and provides further insights into the developing field of headache research.

A Bahra

CORRECTIONS

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A Serrano-Pozo, J Nevado-Portero, G Sanz-Fernández, et al. Spinal anterior artery territory infarction simulating an acute myocardial infarction (J Neurol Neurosurg Psychiatry 2005;76:1584). The authors of this Neurological Picture were mistakenly grouped according to their affiliation. The correct ordering of the authors is: A Serrano-Pozo, J Nevado-Portero, G Sanz-Fernández, E Martinez-Fernández.

doi: 10.1136/jnnp.2004.059212corr1

A Rogoschke-Schumm, H Axer, C Fitzek, et al. Intracerebral haemorrhage in CADASIL (J Neurol Neurosurg Psychiatry 2005;76:1606–7). The authors of this Letter were mistakenly grouped according to their affiliation. The correct ordering of the authors is: A Rogoschke-Schumm, H Axer, C Fitzek, M Dietz, N Peters, J Mueller-Mecke, O W Witte, S Isemann.