COMMENT

Although many neurologists advise steroids and some would recommend acyclovir, the uncertainty regarding the treatment of Bell's palsy is reflected in our questionnaire responses.

The majority of responders indicated that their advice was not based on local guidelines and many commented on the lack of evidence. Some felt it was imperative to discuss the uncertainty with the patient; others that better randomised controlled trials are needed.

A new Scotland based randomised controlled trial will start later this year (Morrison J, personal communication). This study, coordinated by primary care physicians and ear, nose and throat surgeons, will compare four treatment arms (comprising steroids, acyclovir, placebo) within 48 to 72 hours of onset. Assessment of treatment effect will include photographs and questionnaires about objective and subjective outcomes. The aim is to recruit up to 720 patients, of whom 480 will have begun treatment within 48 hours of onset. Given the annual incidence of Bell's palsy in Scotland, the researchers estimate that this will take up to 18 months. Uncertainty in managing this condition can only be resolved by well conducted randomised controlled trials.

M Shaw
Glasgow Royal Infirmary, 10 Alexandra Parade, Glasgow G31 2ER, UK

F Nazir, I Bone
Southern General Hospital, Govan Road, Glasgow

Correspondence to: Dr Monica Shaw; drmonicashaw@hotmail.com

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APPENDIX

Bell's palsy questionnaire

1. How frequently in the last 3 months have you received a query from a GP about treatment of a Bell's palsy? _____
2. Do you arrange to see the patient before giving advice? Yes/No

If you are satisfied with the clinical diagnosis:

3. Would you advise steroids

- within 24 hours? Yes/No
- within 3 days? Yes/No
- within 7 days? Yes/No
- in pregnancy? Yes/No
- with Ramsay Hunt syndrome? Yes/No
- with complete facial palsy (loss of taste/hyperacusis)? Yes/No
- with partial facial palsy? Yes/No

4. If steroids are advised, what regime would you suggest? _____
5. Is the advice you give on steroids based on local guidelines? Yes/No
6. Would you advise acyclovir? Yes/No

If yes:

7. Is the advice you give on acyclovir based on local guidelines? Yes/No
8. Any additional comments:

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Ondine's curse during pregnancy

We report a case of a 34 year old right handed woman seen at 29 weeks' gestation who suffered from apnoea of unknown aetiology. This pregnancy, as well as her first gestation, was complicated by generalised oedema and high blood pressure. Starting at week 25, her husband noticed she had developed intermittent brief periods of apnoea only while sleeping, which lasted as long as one minute but of variable duration. Her husband awakened her each time she had a protracted episode of apnoea. She was asymptomatic while awake. In the 29th week she suffered a more severe apnoea. She was intubated in the field and taken to the hospital for an emergency caesarean section. There was no spontaneous labour. Inability to breathe spontaneously persisted for two weeks postpartum and a neurological consultation was requested.

On initial evaluation blood pressure was 140/90 and the heart rate was 90 beats/min. The neurological examination revealed upbeat nystagmus of small amplitude in the primary position which did not change with upward or downward gaze. She had lack of spontaneous breathing. She was fully awake and cooperative, sitting up in bed with no assistance. While intubated she had an obvious cough reflex but the gag reflex was not formally tested. Tongue examination showed normal movement and power with no evidence of atrophy or fasciculation. Otherwise, cranial nerve and sensorimotor examinations were entirely normal. There was normal tone, with downgoing plantar reflexes and no evidence of other pyramidal findings. There was no record of arrhythmia. No yawning, vomiting, or hiccups were present during the examination and they were not seen by nursing staff.

It was of interest that this patient had suffered from apnoea presenting immediately after her first vaginal delivery two years previously. This was treated with intubation and resolved spontaneously with successful extubation approximately four hours later.

Magnetic resonance imaging of the brain, brain stem, and cervical spinal cord was carried out, and showed a Chiari malformation with tonsillar herniation at C2 level and a cervical syrinx.

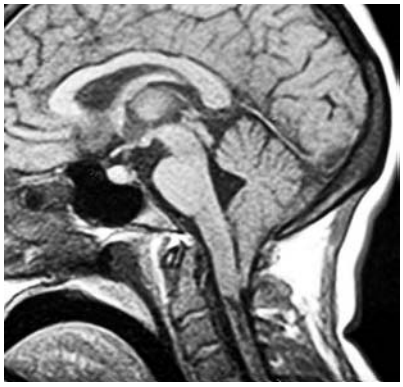

Figure 1 Magnetic resonance imaging of the brain (sagittal section) showing a Chiari malformation with tonsillar herniation at C2 level and a cervical syrinx.

After posterior cranial fossa decompression the patient recovered spontaneous breathing and was off any ventilatory support within six hours. She and her child have been followed for two years following this event. She remains in good health with normal polysomnographic testing.

COMMENT

Ondine's curse is a rare form of central respiratory failure which includes severe sleep apnoea.[1] We describe the case of recurrent sleep apnoea associated with pregnancy and delivery and related to a Chiari malformation that became symptomatic only during pregnancy. We hypothesise that the generalised oedema that occurred during pregnancy, with a potentially mild increase in intracranial pressure, produced dysfunction of central chemoreceptors or the respiratory integrative system of the brain stem. Additionally there may have been compression of the lower cranial nerves, impairing input from peripheral chemoreceptors.[2] Related to this, our patient suffered severe sequelae from a central malformation that was previously clinically inapparent. Although Ondine's curse has rarely occasionally described in patients with Chiari malformation,[3] the expression of secondary sleep apnoea uniquely during pregnancy has not been reported before. Finally we wish to highlight the complete recovery of this patient after posterior fossa decompression, as we found in another published case.[4]

J J Ochoa-Sepulveda, J J Ochoa-Amor
Neurology Department, ''Hospital Universitario Reina Sofia'', 14012 Cordoba, Spain

Correspondence to: Dr Juan Ochoa-Sepulveda; jjos@telefonica.net

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Gender influence on the progression of HTLV-I associated myelopathy/tropical spastic paraparesis

HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a chronic and disabling disease caused by the human T-lymphotropic virus type I. Onset of the disease is insidious and the disease usually progresses slowly over years.[1] However, there have been reports of the rapid evolution of HAM/TSP over months or even weeks. The

basis for these different progression patterns is poorly understood and only a few studies have dealt with this matter.[2] The present study aimed at evaluating a Brazilian HAM/TSP population for possible factors implicated in the progression of the disease.

Methods

We reviewed the files of 338 HTLV-I infected patients evaluated at the outpatient clinic of the Reference Centers for Neurological Infections and HTLV-I, Evandro Chagas Clinical Research Institute (IPEC), FIOCRUZ, Rio de Janeiro, Brazil. Patients were included in the study if they fulfilled the World Heath Organization criteria for HAM/TSP,[1] but were excluded if they had concurrent infections or other disabling diseases that could interfere with clinical progression. The eligible patients were submitted to a clinical questionnaire and physical examination between June 2002 and February 2003. Clinical severity was evaluated using the IPEC disability scale (table 1), which was developed exclusively for the prospective assessment of HAM/TSP.[3] We evaluated clinical progression using a disease progression index (DPI) defined as the IPEC disability final score divided by the duration of the disease, from onset of symptoms, in years. We used this value to divide our sample into quartiles. Patients whose values were under the 25th percentile were called slow progressors and patients whose values were above the 75th percentile were called fast progressors. Both groups were compared for their demographic and clinical characteristics using Fisher's test. DPI values were compared using the Mann-Whitney U test. All p values were two sided and an $\alpha = 0.05$ was employed.

Results

A total of 250 individuals were excluded due to lack of neurological disease or the presence of concurrent infections. The mean age of the remaining 88 individuals was 53.1 years, and there were more women (68.2%) than men. The mean age at onset was 40.7 years and the mean duration of disease was 12.5 years.

Comparison between the fast (n = 22) and the slow (n = 22) progression groups showed a significantly higher prevalence of women in the former group (p = 0.02). Statistical analysis of other variables failed to show significant differences.

To evaluate the possible role of sex hormones in this difference, because the mean age of menopause is around 50 years,[4] we compared men and women according to age at onset of the disease (early onset: <50 years; late onset: ⩾50 years). The mean DPI of women and men were, respectively, 1.79 and 1.17 (p = 0.009) in the early onset group (n = 66; 66% women) and 2.59 and 1.78 (p = 0.731) in the late onset group (n = 22; 68% women), suggesting that women have a faster progression than men if the disease starts before the menopause.

Table 1 The IPEC disability scale

Motor score: Gait
- 0. Normal
- 1. Abnormal but can walk independently
- 2. Abnormal and dependent on eventual unilateral support
- 3. Abnormal and dependent on permanent unilateral support
- 4. Abnormal and dependent on eventual bilateral support
- 5. Abnormal and dependent on permanent bilateral support
- 6. Abnormal, dependent on permanent bilateral support, and occasional use of a wheelchair (WC)
- 7. Permanent use of a WC, stands up, and remains upright without support
- 8. Permanent use of a WC, uses arms to stand up, and remains upright without support
- 9. Permanent use of a WC, needs assistance from others to stand up and remain upright with support
- 10. Permanent use of a WC, unable to stand up, exhibits voluntary movements of the lower limbs when seated
- 11. Permanent use of WC, unable to stand up, and does not have any voluntary movements of the lower limbs

Motor score: Running
- 0. Runs
- 1. Unable to run

Motor score: Climbing stairs
- 0. Climbs
- 1. Climbs only when holding the handrail
- 2. Unable to climb

Motor score: Jumping
- 0. Jumps on one or two feet
- 1. Jumps on two feet, but not with only one
- 2. Jumps on two feet only with hand support
- 3. Unable to jump

Spasticity score: Clonus
- 0. Absent
- 1. Only induced by the examiner
- 2. Spontaneous

Spasticity score: Flexor/extensor spasms
- 0. Absent
- 1. Present

Sensory score: Paresthesias
- 0. Absent
- 1. Present, eventually
- 2. Present, permanently

Sensory score: Lumbar and/or lower limb pain
- 0. Absent
- 1. Present, eventually
- 2. Present during most of the day

Sphincter score: Bladder control
- 0. Total
- 1. Urgency
- 2. Eventual incontinence or retention
- 3. Use of permanent catheter or regular use of relieve catheter

Sphincter score: Bowel continence
- 0. Normal
- 1. Constipation
- 2. Incontinence or total retention, needs manual extraction or enemas

Total: 0–29

Discussion

This is the first study to suggest that HAM/TSP progresses faster in women than in men. This difference seems to be particularly important in women whose disease started before the menopause. Although gender differences regarding the clinical evolution of HAM/TSP have not been reported before, there has been evidence of a disproportional number of women with this disease. Firstly, there is a worldwide female to male preponderance of HAM/TSP patients ranging from 1.5:1 to 3.5:1.[5] Secondly, Nagai *et al* analysed the proviral load of 202 HAM/TSP patients and 243 asymptomatic HTLV-I carriers and found a significantly higher proviral load in female patients when compared to males.[6] It is well known that a higher proviral load is associated with the development of clinical disease.

The reason for the gender difference in our study is unknown, but it is possible that sex hormones play a role in the evolution of the disease. To test this hypothesis, we compared the DPI of patients whose disease had started before and after the age of 50, the mean age of the menopause. The finding of a significantly worse evolution in the female group with early onset of disease, coupled with no significant gender difference being observed in the late onset group, suggests that female hormones may be implicated in HAM/TSP pathogenesis and that their presence at higher levels may be associated with a faster clinical progression. Further support for this idea is provided by the beneficial effects of danazol, an androgenic drug, in the treatment of some HAM/TSP cases.[7]

In summary, we found evidence of worse clinical progression in women with HAM/TSP compared to men. We hypothesise that sex hormones may account for this difference. If confirmed by further studies, this information may lead to a better understanding of the mechanisms involved in HAM/TSP pathogenesis and suggest different treatment options.

M A S D Lima, R B S Bica
Federal University of Rio de Janeiro (UFRJ), Clementino Fraga Filho University Hospital (HUCFF), Rio de Janeiro, Brazil

A Q C Araújo
Reference Centers on Neuroinfections and HTLV, Evandro Chagas Institute of Clinical Research (IPEC), FIOCRUZ, Rio de Janeiro, Brazil

Correspondence to: Marco Antonio S D Lima, 109 Queensberry Street #12, Boston, MA 02215, USA; mdelima@bidmc.harvard.edu

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Plasma VEGF as a marker for the diagnosis and treatment of vasculitic neuropathy

Vasculitic neuropathy is treatable with immunotherapy. However, histological evidence of vasculitis is not always obtained from nerve and muscle biopsies.[1] In particular, in cases of non-systemic vasculitic neuropathy showing no or minimum abnormal findings in serological tests, negative biopsy results cause considerable difficulty in the diagnosis.[1]

Vascular endothelial growth factor (VEGF) is a potent, multifactorial cytokine.[2] VEGF is derived from endothelial cells and pericytes in response to hypoxia, and induces angiogenesis and microvascular hyperpermeability through its binding to VEGF receptors.[2] Vascular involvement by vasculitic neuropathy results in hypoxia. It was reported that VEGF was overexpressed in vasculitic lesions in biopsied sural nerves, and that plasma VEGF levels were found to be raised in dermatomyositis with peripheral neuropathy.[3] These findings suggest that VEGF levels may be increased in patients with vasculitic neuropathy. Although an increase in plasma or serum VEGF concentrations has been reported in some patients with systemic vasculitis,[3] there have been no studies to evaluate plasma VEGF in a series of patients with vasculitic neuropathy. With respect to VEGF levels in neuropathies, a marked increase in serum levels was reported in the Crow-Fukase (POEMS) syndrome.[4] In addition, alterations in VEGF are associated with cancer and diabetes mellitus, and VEGF is involved in the angiogenesis of these diseases.

In this study, we investigated the plasma VEGF concentrations in patients with vasculitic neuropathy in comparison with other neuropathies. After obtaining informed consent, samples were obtained from five patients with vasculitic neuropathy confirmed by muscle or sural nerve biopsies. They all presented with neuropathy as a cardinal manifestation, and included three patients with polyarteritis nodosa, one with vasculitic neuropathy associated with Sjögren syndrome, and one with non-systemic vasculitic neuropathy. None of the patients were on drug treatment at the time of sampling. After disease remission was achieved by treatment with corticosteroids or other immunosuppressants, we analysed plasma VEGF again in three of the patients, including two with polyarteritis nodosa and one with Sjögren syndrome. As a control group, we used plasma from 18 age matched healthy volunteers, eight patients with Guillain-Barré syndrome, five with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and seven with amyotrophic lateral sclerosis, after obtaining informed consent. Patients with diabetes mellitus or cancer were not included in the study.

Venous blood was sampled into an EDTA tube with minimal stasis. The sample was centrifuged and the plasma VEGF concentration was determined by a quantitative sandwich-enzyme immunoassay technique using a Quantikine kit (R&D Systems, Minneapolis, Minnesota, USA). As VEGF is secreted by platelets in the clotting process,[5] we measured plasma samples, not sera, to evaluate the circulating VEGF level precisely.

Differences between the groups were tested by the Kruskal–Wallis test and the Mann–Whitney U test. Differences were considered significant when the probability (p) value was <0.05. Significance tests for group differences were computed with StatView v5.0 (SAS Institute, Cary, North Carolina, USA).

The mean (SD) plasma VEGF concentrations in patients with vasculitic neuropathy (303 (182) pg/ml) were significantly higher than in the healthy controls (30.9 (31.7) pg/ml) ($p<0.01$) as well as in patients with Guillain-Barré syndrome (85.7 (57.3) pg/ml) ($p<0.05$), CIDP (49.9 (48.3) pg/ml) ($p<0.05$), and amyotrophic lateral sclerosis (88.1 (55.7) pg/ml) ($p<0.05$) (fig 1). There was no statistical difference in plasma VEGF concentrations between healthy controls and patients with CIDP, Guillain-Barré syndrome, or amyotrophic lateral sclerosis. The plasma VEGF concentrations in patients with vasculitic neuropathy before treatment (423 (97.1) pg/ml) decreased significantly after successful treatment with corticosteroids or other immunosuppressants, to 150 (114) pg/ml ($p<0.05$). One case with polyarteritis nodosa and the patients with vasculitic neuropathy associated with Sjögren syndrome had a marked decrease in plasma VEGF after treatment (from 461 to 91.3 pg/ml and from 496 to 77.8 pg/ml, respectively). In the other patient with polyarteritis nodosa, the plasma VEGF levels decreased mildly, from 313 to 281 pg/ml.

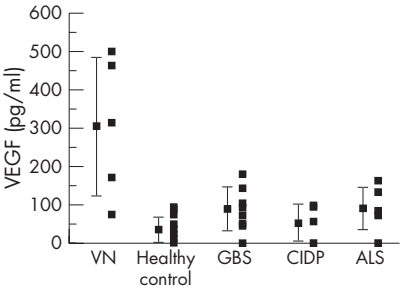

Figure 1 Plasma levels of vascular endothelial growth factor (VEGF) in patients with vasculitic neuropathy (VN), healthy controls, Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and amyotrophic lateral sclerosis (ALS).

COMMENT

Our results indicated that increased plasma VEGF could be a useful marker for the diagnosis of vasculitic neuropathy and for monitoring a therapeutic effect.

This is the first report to show a significant increase in plasma VEGF levels in patients with vasculitic neuropathy compared with other neuropathies. As our patients with vasculitic neuropathy did not have cancer or diabetes mellitus, and as the plasma VEGF concentrations were significantly decreased after treatment, we consider that VEGF would be secreted into blood by the vasculitic lesions in this conditions. We could find no significant increase in plasma VEGF levels in CIDP, Guillain-Barré syndrome, or amyotrophic lateral sclerosis. Vasculitic neuropathy may present with clinical manifestations similar to CIDP or other peripheral neuropathies.[1] The increase in plasma VEGF could be a helpful marker to distinguish vasculitic neuropathy from CIDP and other peripheral neuropathies in such patients.

Although our results indicate the potential value of plasma VEGF as a marker in the diagnosis and treatment of vasculitic neuropathy, the significance of the results is limited by the relatively small number of patients. Further studies with a larger study population are necessary to confirm our results.

K Sakai, K Komai, D Yanase, M Yamada
Department of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Science, Kanazawa 920-8640, Japan

Correspondence to: Dr K Sakai; ksakai@med.kanazawa-u.ac.jp

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Acute aspiration pneumonia due to bulbar palsy: an initial manifestation of posterior fossa convexity meningioma

False localising signs of intracranial lesions are defined as signs not generally associated with disturbances of function at the site of