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Chronic intestinal pseudo-obstruction as the initial feature of pure autonomic failure

Chronic intestinal pseudo-obstruction (CIP) is a rare and highly morbid syndrome characterised by impaired gastrointestinal propulsion together with symptoms and signs of bowel obstruction in the absence of any lesions occluding the gut lumen (tumours, adhesive peritonitis, and so on).[1] CIP is thought to have two forms: myogenic and neurogenic.[1] Comorbid urinary retention may also occur.[2] Postural hypotension is not a feature in CIP. However, we recently had such a CIP patient with profound postural hypotension, which was detected only by a head up tilt test, and he was finally diagnosed as pure autonomic failure (PAF).

Case report

A 59 year old man gradually (over two months) developed intractable nausea and vomiting immediately after taking meals, although he did not have dysphagia. He also had abdominal distension, discomfort, and mild difficulty in defaecation. At that time, he had no features to suggest autonomic failure affecting other systems than the gut, such as postural dizziness or genitourinary dysfunction. Six months later, he was admitted to a gastrointestinal surgery hospital because of these symptoms, at which time he was emaciated. However, gastric and colonic endoscopy showed no organic lesions. As abdominal *x* ray findings continued to support the suspicion of intestinal obstruction, a partial colectomy (ileo-cecum and sigmoid colon) was carried out. However, the resected colon specimen showed no organic lesions such as a tumour, and his bowel symptoms persisted. In addition, after his indwelling urinary catheter was removed, the patient was unable to urinate and was taught to perform clean, intermittent self catheterisation (four times a day). The patient visited another gastroenterology hospital where he was shown to have delayed gastric transit. Based on these findings, he was diagnosed as having CIP. Treatment with prokinetic drugs such as itopride hydrochloride (a peripheral dopamine D2 receptor antagonist) and mosapride citrate (a peripheral 5-HT4 receptor agonist) caused his vomiting and abdominal discomfort to be moderately ameliorated.

Seven months later, because he still had bowel and urinary dysfunction, he was referred to our hospital. Neurological examination was completely normal. Bedside systolic pressure fall on standing was small (16 mm Hg, from 142 to 126) with an increase in heart rate (22 beats/min, from 60 to 82), and he had no dizziness. Routine laboratory data and a cerebrospinal fluid examination were normal. Anti-Hu antibody and anti-nuclear antibodies were negative. Nerve conduction studies were normal in the upper and lower limbs. Brain magnetic resonance imaging (MRI) was normal. Although he had had no episodes of postural or postprandial dizziness or syncope during the course of his illness, a head up tilt test (60° for 10 minutes) resulted in a systolic blood pressure fall of 53 mm Hg (from 178 to 125; normal <20) with a heart rate increase of 29 beats/min (from 51 to 80).[3] Plasma noradrenaline was 44 pg/ml (normal >100) in the supine position and 83 pg/dl after the head up tilt.[3] Although he had no complaints relating to his eyes, diluted noradrenaline and pilocarpine instillation showed denervation supersensitivity in the pupil. He did not have sicca symptoms. Since he had urinary retention, we undertook electromyography (EMG) cystometry, done according to the standards of the International Continence Society (Janus, Lifetec Inc, Houston, Texas, USA). He could not urinate because of an acontractile detrusor and non-relaxing sphincter. In addition, the patient had completely lost first bladder sensation (>600 ml; normal, 100 to 300). Although he reported that his erection was normal, Rigiscan Plus (Timm Medical Technologies Inc, Minnesota, USA) showed markedly decreased nocturnal penile tumescence. Under cessation of the prokinetic drugs, we also carried out gut function tests following the standards set by the American Gastroenterological Association, using electrogastrography (Nipro Inc, Osaka, Japan), a colonic transit time (CTT) test (Sitzmarks; Konsyl Pharmaceuticals Inc, Edison, New Jersey, USA), and recto-anal videomanometry (Janus, Lifetec Inc),[4] even though he had undergone the partial colectomy. The electrogastrography did not show the postprandial or diurnal acceleration that were observed in normal subjects. The patient had a prolonged total CTT of 72.0 hours (normal 16.0 to 48.0). In the videomanometry, during rectal filling with contrast medium (50 ml/min), he did not have the phasic rectal contractions that are observed in normal subjects. All these findings confirmed the diagnosis of PAF.

Comment

Our patient had initially been diagnosed as having CIP because he had abdominal distension without any organic lesions on gastric and colonic endoscopy.[1] CIP can be classified as either secondary to a wide array of recognised pathological conditions or idiopathic. The known mechanisms of CIP include "myogenic" and "neurogenic" types.[1] In myogenic CIP, vacuolar degeneration and fibrosis of the muscularis propria occur (also known as visceral myopathy). De Giorgio *et al*[1] further classified neurogenic CIP into two forms: *inflammatory neuropathies*, in which a significant inflammatory/immune response is identified within the myenteric ganglia (anti-Hu antibody-positive CIP, vasculitis associated CIP, and so on); and *degenerative neuropathies*, characterised by evidence of neurodegenerative aspects or mitochondrial abnormalities. It is noteworthy that our CIP patient had postural hypotension suggestive of generalised autonomic failure, which was detected only by a head up tilt test, and he was finally diagnosed as having PAF. PAF is an idiopathic sporadic disorder characterised by postural hypotension, but usually with more widespread autonomic failure including bowel and bladder dysfunction.[3 5] No other neurological features are present, such as gait difficulty or numbness, distinguishing this disorder from multiple system atrophy or amyloid neuropathy. Postural hypotension is usually the initial and presenting feature in PAF. However, when postural hypotension progresses insidiously and the systolic blood pressure on standing is maintained above 100 mm Hg, postural hypotension might not make itself obvious to the patient. Thus postural blood pressure should be checked to determine the extent of autonomic abnormalities in CIP.

Our case suggested that testing for postural hypotension should be carried out determine the extent of autonomic abnormalities in CIP, as PAF may present with CIP as the first or presenting symptom.

Y Yamanaka, R Sakakibara, M Asahina, T Uchiyama, Z Liu, T Yamamoto, T Ito, T Suenaga
Department of Neurology, Chiba University, Chiba, Japan

T Odaka, T Yamaguchi
Department of Gastroenterology, Chiba University

K Uehara
Department of Gastroenterology, Konodai Hospital, Ichikawa, Japan

T Hattori
Department of Neurology, Chiba University

Correspondence to: Dr Ryuji Sakakibara, Neurology Department, Chiba University, 1-8-1 Inohana Chuo-ku, Chiba 260-8670, Japan; sakakibara@faculty.chiba-u.jp

doi: 10.1136/jnnp.2005.079905

Competing interests: None declared.

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Remission of chronic inflammatory demyelinating polyneuropathy after alemtuzumab (Campath 1H)

We describe a patient with intravenous immunoglobulin (IVIg) dependent relapsing chronic inflammatory demyelinating polyneuropathy (CIDP), unresponsive to steroids or conventional immunosuppressive agents, who achieved remission following treatment with alemtuzumab.

A 19 year old women presented with a two week history of distal lower limb paraesthesiae and distal upper limb weakness. Her symptoms worsened over four weeks but she remained mobile. There was no history of preceding infections, pain, or autonomic dysfunction. Examination revealed reduced limb muscle tone and distal weakness, more marked in the upper limbs. She was areflexic with flexor plantar responses and had

reduced pin prick sensation in the hands and toes.

A lumbar puncture showed a raised protein of 1.8 g/l, with normal glucose and cell counts and negative oligoclonal bands. A preliminary diagnosis of Guillain-Barré syndrome was made and she was treated conservatively, with good recovery.

Three months later she developed further weakness, predominantly affecting her legs. Examination revealed normal muscle tone, distal but asymmetrical limb weakness, absent reflexes, and distal sensory loss. She remained mobile with the aid of unilateral support.

Further investigations were normal or unremarkable; these included full blood count, blood film, urea and electrolytes, liver function tests, glucose, erythrocyte sedimentation rate, creatinine kinase, vitamin B-12, folate, serum electrophoresis, antinuclear antibodies, antineutrophilic cytoplasmic antibody, antiganglioside antibodies including anti-GM1, anti-double-stranded DNA antibodies, HIV, hepatitis A, B, and C, and urinary porphyrins. Genetic testing for hereditary neuropathy with liability to pressure palsies, CMT-1a and PMP-22 was unremarkable. Nerve conduction studies showed absent sensory responses in the arms and an absent sural response, but normal right superficial peroneal nerve response. Motor conduction velocities were reduced to 13–25 (mean 19) m/s with evidence of conduction block.

One week after a five day course of IVIg (Octagam 22 g/day) she had improved significantly, with only mild residual distal weakness in the upper limbs. She was well for one month before suffering a further relapse, with a similar clinical pattern, and received a further course IVIg with good response. The diagnosis was revised to CIDP. No nerve biopsy was undertaken as the presentation was considered typical and confounding diagnoses had been excluded.

After several further relapses she was started on oral prednisolone, without benefit. Later introduction of azathioprine provided an initial partial response only. Eighteen months after disease onset the patient had experienced 11 relapses during which she was unable to walk unaided, with an average interval of seven weeks between IVIg treatments, and she had also developed wasting of the small hand muscles. After detailed discussion of treatment options and when written consent had been obtained she was treated with a five day infusion of alemtuzumab (30 mg/day), from which she experienced no significant side effects. Two further relapses occurred, at five weeks and eight and a half weeks post-treatment, both successfully managed with IVIg. Her tendon reflexes returned and sensory deficit resolved, but some mild distal upper limb weakness remained. Oral prednisolone and azathioprine were withdrawn at 4.0 and 6.5 months respectively. The patient remained well for 16 months, but then suffered a further relapse, which was treated with IVIg with good response. A subsequent relapse occurred after 10.5 weeks, again treated with IVIg. A second course of alemtuzumab has recently been given (fig 1). Longitudinal neurophysiological studies did not correlate with clinical recovery.

Pretreatment lymphocyte subsets showed that 73.5% of lymphocytes were CD3+, 18.4% CD4+. It was not possible to assess lymphocyte subsets post-treatment as the total lymphocyte count was only 0.16 ($\times 10^9$/litre) but return to normal levels corresponded with a return of clinical activity.

The exact pathogenesis of CIDP is unknown. Pathological studies have shown T cell infiltrates on biopsies of peripheral nerves and in necropsy studies, and increased levels of interleukin 2 receptors and circulating activated peripheral T lymphocytes.[1]

Traditionally steroids have been the mainstay of treatment for CIDP, and their usefulness was recently confirmed in a Cochrane review. IVIg has been shown to be an effective but short lived treatment, with two thirds of patients responding; however, 60–70% require repeated courses. IVIg is expensive and associated with potentially serious side effects. Plasma exchange is considered as effective as IVIg. Various other drugs have been used in small numbers of patients, including azathioprine, cyclophosphamide, methotrexate, ciclosporine A, mycophenolate mofetil, and interferons. A Cochrane review recently evaluated these and concluded there was inadequate evidence to determine benefit.[2] One other case report describes the use of monoclonal antibodies in CIDP, documenting a clear response to rituximab.[3]

Alemtuzumab (Campath 1-H) is a monoclonal antibody used for the treatment of B cell chronic lymphocytic leukaemia and multiple sclerosis. It targets CD52 antigen and is thought to have a role in immune modulation. CD52 is a low molecular weight glycoprotein present on most lymphocyte lineages, monocytes, and some cells in the male reproductive system. Monoclonal antibodies directed against CD52 cause complement mediated lysis and reduce the numbers of circulating lymphocytes,[4] which may explain the therapeutic effect seen in our patient.

Alemtuzumab has been associated with various side effects, including autoimmune thyroid disease, reported in a third of treated patients with multiple sclerosis. In a study of patients receiving alemtuzumab along with fludarabine and melphalan, followed by stem cell transplantation for treatment of haematological malignancies, five of 85 patients developed a progressive peripheral sensorimotor radiculoneuropathy. However, there have been no reports of similar complications in patients treated with alemtuzumab as part of conventional allograft[5] or in patients with multiple sclerosis. The main reported side effects are infusion related, such as hypotension, fever, shortness of breath, and rash.

It is unclear why our patient had two relapses in the eight weeks following treatment with alemtuzumab. Effects on circulating T lymphocytes and monocytes following infusion are rapid, with a single dose of alemtuzumab causing depletion of CD8+ T cells for 30 months and CD4+ T cells for 60 months on average. However, it is likely that the mechanism of alemtuzumab's efficacy is probably not T cell depletion but rearrangement of the lymphocyte repertoire. It may be that extravascular activated lymphocytes are already primed for the pathological process and it is not until further recruitment of cells from the intravascular space is demanded that the disease process is slowed. The length of remission approximates to the time course of this drug's effectiveness in multiple sclerosis,[6] in which relapses are also observed in an eight week window following treatment before disease remission.

This case report shows the potential usefulness of monoclonal antibodies as a novel treatment for severe relapsing CIDP. Further studies are needed to evaluate this as a future treatment option.

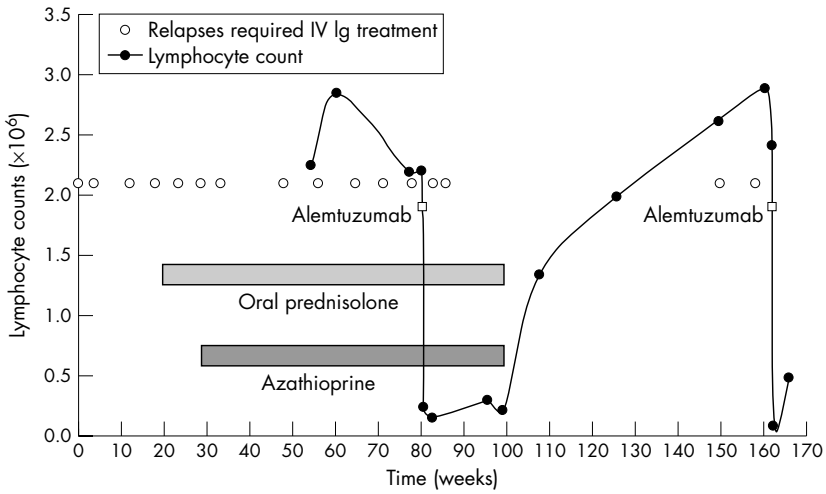

Figure 1 Graph showing the relation of relapses requiring hospital admission and intravenous immunoglobulin (IVIg) to treatment with prednisolone, azathioprine, and alemtuzumab and the lymphocyte count.

C Hirst
Helen Durham Neuro-inflammatory Centre, Department of Neurology, University Hospital of Wales, Heath Park, Cardiff, UK

S Raasch
Department of Clinical Neurophysiology, University Hospital of Wales

G Llewelyn
Department of Neurology, University Hospital of Wales, Heath Park, Cardiff CF14 4XN

N Robertson
Helen Durham Neuro-inflammatory Centre, Department of Neurology, University Hospital of Wales

Correspondence to: Dr Claire Hirst, Helen Durham Neuro-inflammatory Centre, Department of Neurology, University Hospital of Wales, Heath Park, Cardiff CF14 4XN, UK; clairewarren_uk@yahoo.co.uk

doi: 10.1136/jnnp.2005.076869

Competing interests: None declared.

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Simultaneous occurrence of neuromyotonia and morphoea: a cause–effect relationship?

A Kumar, R Jain
Department of Neurology, Wockhardt Brain and Spine Hospital, Mulund-Goregaon Link Road, Mulund West, Mumbai, Maharashtra, India

J Daga
Department of Internal Medicine, Icon Hospital, Dombivli East, Maharashtra, India

Correspondence to: Ajit Kumar, Department of Neurology, Wockhardt Brain and Spine Hospital, Mulund-Goregaon Link Road, Mulund West, Mumbai 400071, Maharashtra, India; kumar_ajit71@rediffmail.com

doi: 10.1136/jnnp.2005.083683

Competing interests: None declared.

Informed consent was obtained for publication of figures 1 and 2.

We report a case of unusual occurrence of neuromyotonia and morphoea (localised scleroderma) simultaneously in the same limbs. The patient was a 32-year-old man who presented with a 2-year history of twitching muscles in the right limbs with loss of hair and tightness of skin in the same limbs. Examination showed an almost complete loss of hair on the right arm, forearm and hand (fig 1). He also had hair loss on the right lower limb, especially on the back of the thigh and calf (fig 2). The skin in these areas seemed to be stretched and shiny with a parchment-like appearance. The other remarkable feature on examination was myokymia of the right-sided biceps, triceps, deltoid, brachioradialis, hamstrings and calf muscles. The rest of the neurological examination was normal. The clinical diagnosis was morphoea associated with neuromyotonia.

The antinuclear antibody was weakly positive. Anti-SCL-70 and anti-JO-1 antibodies were negative. CT scan of the chest was normal. Results of nerve conduction and repetitive nerve stimulation studies were normal. Examination by needle electromyography of the right deltoid, biceps, triceps and brachioradialis showed increased spontaneous activity, with single, doublet, triplet and long bursts of single motor unit potentials at rest (fig 3). Very long bursts (up to 60 s) of motor unit potentials akin to voluntary contraction were seen at rest in the right vastus lateralis. Needle electromyographic findings of the muscles of the left limbs were normal. The result of skin biopsy from the affected area in the right arm showed a thinned out epidermis with hyperkeratinisation, with atrophic changes in the fibrous connective tissue in the dermis. Collagenisation and compression of fibrous tissue into dense compact collagen masses was seen in the dermis. Bundles of thickened nerves with round cell infiltrates were observed. These observations gave an impression of morphoea. A marked improvement in the neuromyotonia was noted within a fortnight of starting treatment with 300 mg/day phenytoin. No immunomodulatory treatment was considered because of the excellent response to phenytoin.

The most remarkable feature in our patient was the spatial and temporal coincidence of morphoea and neuromyotonia. This suggests an arcane relationship between the two conditions. The motor axon being the possible site of origin of neuromyotonia,[1 2] one possible mechanism could be pathological change of nerves due to scleroderma.[3] The appearance of nerve endings in the skin biopsy specimen lend credence to this view.

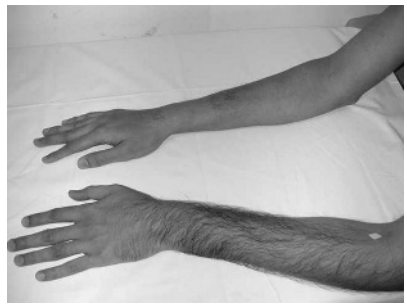

Figure 1 Forearms and hands of the patient showing lack of hair on the right side.

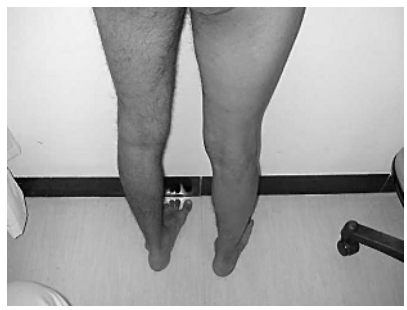

Figure 2 Back of thighs and legs of the patient, showing lack of hair on the right side.

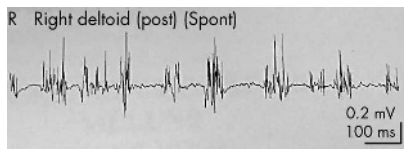

Figure 3 Needle electromyographic findings of the right deltoid showing motor unit potentials at rest.

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Ear dyskinesia

Focal or segmental dyskinesias and dystonic syndromes affecting the cranial muscles are well recognised. Examples include the well known oro-bucco-facial dyskinesia caused by the long term use of neuroleptics, Meige syndrome, oromandibular dystonia, and blepharospasm. Among focal dyskinesia, ear dyskinesias are extremely uncommon and only a few cases have been reported.[1 2]

Case report

We report a 57 year old women who complained of involuntary movements of both ears for a year. The movements were initially intermittent but progressively became continuous. She could not control them voluntarily. The movements disappeared during sleep. There was no history of local trauma or neuroleptic treatment. Three months before onset, she had received paroxetine for depression. On examination there was a semirhythmic synchronous elevation and retraction of both ears. Movements were also seen in the skin around the ear. There was an intermittent contraction of frontal muscles as well. On clinical examination, there was amimia, and slow bilateral alternating serial movements. There were no tremor or hypertonia. MRI of the brain was normal. Electromyography of the left auricularis superior muscle showed bursts of normal motor unit potentials lasting 280 ms at a frequency of 2 Hz. The patient responded well to local injections of botulinum toxin type A (Botox) into the auricularis superior and posterior muscles (40 MU). The toxin was injected without EMG monitoring.

Discussion

The clinical appearance of our patient's movement disorder closely resembles dyskinesia because it consists of stereotyped focal or segmental movements affecting the ears and lasting for a few seconds or so. Focal dyskinesia can affect various regions of the body: ear, back, shoulder girdle and upper