LETTERS

Increased arterial carboxy-haemoglobin concentrations in patients with sporadic amyotrophic lateral sclerosis

Carbon monoxide is endogenously produced by enzymes known as haem oxygenase (HO). The CO produced is immediately bound to blood haemoglobin as carboxyhaemoglobin (Hb-CO). HO-1, the inducible form of HO, is induced by various stimuli, including reactive oxygen species (ROS) and proinflammatory cytokines.¹ Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease in humans that results in the selective death of both upper and lower motor neurones. ROS have been implicated in the mechanism of neuronal injury in ALS, based on the evidence that mutations of the superoxide dismutase (SOD) gene have been identified in patients with familial ALS, and that transgenic mice with mutated SOD genes have an ALS-like phenotype.² Furthermore, increased oxidative damage has been found in spinal motor neurones of necropsy samples from both sporadic and familial ALS patients.² This suggests that with the progression of neuronal injury the spinal cord in ALS patients may induce HO-1, leading to the

production of CO, followed by increased concentrations of blood Hb-CO. Indeed, immunohistochemical studies have shown increased HO-1 expression in spinal motor neurones in ALS patients and animal models of ALS.³ However, blood Hb-CO in ALS patients has not been examined. We investigated arterial Hb-CO concentrations in relation to disease progression in patients with sporadic ALS (SALS) and controls.

The subjects were 21 patients with SALS (16 men, 5 women) with a mean (SD) age of 61.5 (12.8) years, and 20 healthy age matched controls (17 men, 3 women) aged 61.2 (11.8) years. The diagnosis of SALS was based on neurological history, neurological examination, and laboratory tests. When their condition was stable, the functional disability of the disease was evaluated using the ALS score developed by Norris,⁴ which ranges from 0 (maximum impairment) to 100 (normal). The blood samples for analysis of Hb-CO, arterial blood gas tensions, and spirometric data were obtained at the same time as the ALS score evaluation. Arterial Hb-CO concentration was measured with a spectrophotometer as previously described.⁵ Controls were recruited by advertisement as volunteers, and none was receiving long term drug treatment or had a history of chronic neural, muscular, or pulmonary disease. None of the patients or controls had any inflammatory diseases such as common

colds, sinusitis, or bronchitis. All subjects in the study were non-smokers. We informed the subjects of the aims and content of the study, and obtained their consent for their participation.

Age and sex did not differ significantly between controls and patients with SALS. Vital capacity and forced expiratory volume in one second were significantly lower in patients with SALS (78.2 (9.3)% of predicted ($p<0.05$), and 86.0 (8.0)% of predicted ($p<0.01$), respectively) than in control subjects (96.2 (8.6)% and 95.4 (9.8)% of predicted). As shown in the fig 1A, arterial Hb-CO concentrations in patients with SALS were higher than in the control subjects, at 1.10 (0.62)% v 0.65 (0.20)% ($p<0.01$ by Wilcoxon rank-sum test). Moreover, arterial Hb-CO concentrations in patients with SALS showed a significant inverse correlation with ALS score by Pearson's correlation test ($r = -0.76$, $p<0.05$) (fig 1B). Neither arterial O₂ tension (mean 89.7 (7.2) torr) nor arterial CO₂ tension (mean 44.5 (11.5) torr) was significantly correlated with ALS score in patients with SALS ($r = -0.05$, $p = 0.85$; and $r = 0.06$, $p = 0.82$, respectively).

In six of the 21 patients with SALS, we were able to re-evaluate the ALS score and arterial Hb-CO concentrations six months after the first evaluation. Of the remaining 15 patients, four had died before re-evaluation, nine had changed hospital, and two discontinued attendance at our clinic for unknown reasons. In the six patients re-evaluated, arterial Hb-CO concentrations were significantly raised at the second evaluation ($p<0.05$), while the ALS score was significantly lower ($p<0.05$) (Wilcoxon matched pairs signed rank-sum test (fig 1C)). Arterial O₂ and CO₂ tensions were not significantly different between the first and second evaluations (90.7 (7.0) v 84.9 (10.2), $p = 0.30$; and 43.3 (8.0) v 38.5 (2.0) torr, $p = 0.51$, respectively).

Comment

In this preliminary study, we showed increases in arterial Hb-CO concentrations in patients with SALS. The increased Hb-CO concentration correlated with the severity of the disease and, within individuals, changed with the progression of the disease. In a follow up study, we were able to re-evaluate only six of the initial 21 patients. It is therefore possible that there was selection bias—for example, the capacity to produce a higher Hb-CO level might have affected mortality. A larger sample size and more frequent follow up are needed to clarify this. Arterial blood gas tensions had no significant relation to the severity of ALS in our patients, suggesting that the increase in Hb-CO level is unlikely to be a sign of early respiratory failure in SALS. Our observations might suggest that the Hb-CO produced reflects the degree of neuronal injury in ALS.

Arterial Hb-CO concentration is reported to be raised in inflammatory respiratory diseases.⁵ Although the level of Hb-CO concentration in SALS is equivalent to that in inflammatory respiratory diseases, laboratory data—such as C reactive protein and peripheral white blood cell count—failed to show any inflammatory evidence in SALS, in contrast to pneumonia and idiopathic pulmonary fibrosis, which cause a prominent inflammatory response.³ This suggests a different mechanism of HO-1 induction between ALS and inflammatory respiratory

Figure 1 Arterial carboxyhaemoglobin concentrations (Hb-CO) with disease progression in sporadic amyotrophic lateral sclerosis (SALS). (A) Arterial CO-Hb concentration in controls (n = 20) and in patients with SALS. Vertical bars show SD. (B) Relation between arterial Hb-CO concentration and ALS score in patients with SALS. ALS scores correlated significantly with arterial Hb-CO concentrations ($p<0.01$). (C) Change in arterial Hb-CO concentrations (left) and ALS scores (right) in patients with SALS between the first and second evaluation (six months interval). There were significant differences in arterial Hb-CO concentrations ($p<0.05$) and ALS scores ($p<0.05$) in patients with SALS between the two evaluations by Wilcoxon signed rank test. * $p<0.05$ v control by Wilcoxon rank-sum test.

diseases. Arterial Hb-CO concentrations in other neurodegenerative diseases need to be investigated to clarify the disease specificity of Hb-CO elevation. Although further large cohort studies are required, arterial Hb-CO concentration may be useful for objective monitoring of disease progression in ALS.

H Yasuda, S Ebihara, M Yamaya, M Asada, H Sasaki

Department of Geriatric and Respiratory Medicine, Tohoku University School of Medicine, Sendai 980-8574, Japan

M Aoki

Department of Neurology, Tohoku University School of Medicine

Correspondence to: Dr Satoru Ebihara, Department of Geriatric and Respiratory Medicine, Tohoku University School of Medicine, Seiryō-machi, Aoba-ku, Sendai, 980-8574, Japan; satoru_montreal@hotmail.com

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The red ear syndrome

The red ear syndrome (RES) was described by Lance,¹ who suggested associations with upper cervical disorders and atypical trigeminal and glossopharyngeal neuralgias. Recently, Raieli et al² underlined the close temporal relationship between RES and migraine.

Patient 1

A 22 year old man, with a 12 year history of migraine without and with aura, experienced acute onset of burning and painful ear without other autonomic symptoms. These symptoms were always homolateral to the hemicrania and persisted for about two hours. The RES could be preceded by a headache. He also described sudden attacks of isolated burning ear without headache or autonomic symptoms. This isolated RES was limited to one side and could occur on either side with no preference for one side or the other. The attacks were not related to any particular stimulus. They occurred three or five times a month; approximately half of the episodes were followed by a migraine attack without aura.

Patient 2

A 92 year old woman experienced, 18 years ago, attacks of burning and red left ear associated with autonomic signs, such as left lacrimation. The attacks lasted for 20 minutes to two hours and could occur every day for 15-45 days every 12-18 months. No precipitating factor was found, and the attacks were resistant to non-steroidal anti-inflammatory drugs (indometacin).

Subcutaneous sumatriptan was not given because of the age of the patient.

Neurological examination and brain magnetic resonance imaging (MRI) of both patients were normal.

Discussion

Patient 1 appeared to fit the criteria for RES as described by Raieli et al.² This type of RES occurs more frequently in children than in adults and is associated with a history of migraine with or without aura and of painful and red ear, unilateral or alternating, in isolation or associated with migraine attacks. This hypothesis was previously suggested by Hirsch³ who reported unilateral and bilateral RES episodes in patients with "vascular headaches". Patient 2 was thought to have trigeminal autonomic cephalgia (TAC).

Despite common elements, the two patients with RES described here differed in age, associated disorders, as well as the response to therapy.

Two different types of RES can be described: the first type occurs in children or young people and is clearly correlated with migraine.² These cases can be considered to be idiopathic. The second type occurs in adults and is associated with upper cervical disorders¹ or with TAC. RES has been described in association with diverse etiologies: migraine,² upper cervical disorders and temporomandibular joint dysfunction,¹ and TAC, in particular short acting, unilateral headache attacks with conjunctival injection and tearing (SUNCT), and hemicrania continua.⁴⁻⁶ These associations suggest a common pathophysiological mechanism with activation of the trigeminovascular system. This variability occurs despite the belief that the final common pathway (the trigeminal-autonomic reflex) is presumably the same as in cluster headache.⁷

The trigeminal-autonomic reflex pathway consists of a brainstem connection between the trigeminal nerve and facial parasympathetic outflow.⁷ RES ear episodes can be mediated by a cervico-autonomic reflex due to either an upper cervical disorder, or directly by trigemino-autonomic stimulation via the auriculotemporal nerve.² Trigemino-vascular activation may produce pain that extends beyond the trigeminal territory. Thus the innervation of the earlobe, which is predominantly from the second and third cervical roots, can explain the association with upper cervical disorders.

A Donnet

Service de Neurochirurgie, Hôpital la Timone, Marseille, France

D Valade

Centre d'Urgence Céphalée, Hôpital Lariboisière, Paris, France

Correspondence to: Dr A Donnet, Service de Neurochirurgie, Hôpital la Timone, 264 bd Saint Pierre, 13385 Marseille Cedex 05, France; adonnet@AP-HM.fr

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Arteriovenous fistula of the superficial temporal artery: an exceptional complication of the pterional approach

Despite the widespread use of the pterional approach in neurosurgical procedures, complications due to iatrogenic injuries of the superficial temporal artery (STA) are extremely rare. Iatrogenic pseudoaneurysms of the STA have been reported as a complication of craniotomy,¹ secondary to placement of external ventricular drainage catheters² or of a pin type headholder device.³ Reported cases of iatrogenic arteriovenous fistula of the STA have occurred after hair transplantation⁴ and after temporomandibular arthroscopy.⁵ We report a case of iatrogenic arteriovenous fistula of the STA after pterional craniotomy. To the best of our knowledge, such a complication of craniotomy has not been reported before.

A 53 year old man was initially referred to our department with a grade 3 WFNS (World Federation of Neurological Surgeons) subarachnoid haemorrhage. Cerebral angiography revealed an anterior communicating artery aneurysm. A right pterional craniotomy was performed to clip the aneurysm. The superficial temporal artery was incised through a skin incision 7 cm above the tragus, and was coagulated carefully. The surgical procedure and postoperative course were uneventful, and the patient was discharged after two weeks with mild cognitive disturbances. Two months later, he complained of pulsatile tinnitus in the right ear. The tinnitus was exacerbated by lying on the right side. On physical examination, a thrill was palpable and a continuous murmur with systolic accentuation was audible on the pterional scalp incision above the tragus. The murmur and the thrill were abolished by compression of the proximal superficial temporal artery. Selective right external carotid artery angiography revealed an arteriovenous fistula between the main branch of the right STA and the homologous vein (fig 1). An internal carotid artery angiography was also performed, mainly to control the aneurysm, which showed no evidence of any contribution from the intracranial circulation. At operation, the arteriovenous fistula was proximally and distally ligated and excised completely. Postoperatively, the tinnitus disappeared, and the patient was discharged three days later. Six months after surgery there was no sign of recurrence.

Arteriovenous fistulas of the STA are rare lesions that occur most often after trauma or apparently spontaneously. The latent period between STA injury and the presentation of symptoms ranges from some days to 15 years. The presenting symptom usually includes a

Figure 1 Selective right external carotid artery angiography revealing an arteriovenous fistula between the main branch of the right superficial temporal artery and the homologous vein.

pulsatile, painless, expanding mass in the temporal region. The lesion may be accompanied by headache, pulsatile tinnitus, or dizziness. On physical examination, a palpable thrill and/or an audible continuous murmur may be detected. The murmur usually disappears or diminishes with proximal STA compression. In our case, the diagnosis of arteriovenous fistula of the STA was clinically obvious. However, an angiography of the external carotid artery was useful for surgical planning and demonstration of the feeding and draining vessels. The treatment of arteriovenous fistula of the STA is ligation and surgical excision, but successful endovascular embolisation of the fistula has also been reported.⁵ The latter treatment seems recommendable, because it is less aggressive and can be performed at the same time as angiography.

In fashioning the scalp flap for the pterional craniotomy, an injury to the STA is almost inevitable. Care must be taken in coagulation, or it might be preferable to ligate the incised stump. We suppose that, in our case, partial injury to the wall of the STA and the adjacent venous structures during suturing the wound, especially around tragus where the STA lies just beneath the skin incision, may have caused of the development of the fistula. We propose that arteriovenous fistula of the STA should be added to the list of possible complications following a pterional approach.

S F A Amlashi, L Riffaud, X Morandi

Department of Neurosurgery, Rennes University Hospital, France

Correspondence to: S F A Amlashi; amlashi@yahoo.com

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Local pain during REBIF injection is not due to acidic pH

In our clinical experience, local pain at the injection site is a common adverse event for persons with MS receiving subcutaneous REBIF (interferon- β 1a) injections. Most of our patients experiencing this describe a moderate burning or stabbing pain during injection, that may persist for a few minutes. These reactions vary among individuals and also for the same individual on different occasions. The acidic pH of REBIF, which is necessary to ensure stability of the IFN- β 1a solution, is considered a possible cause of pain. We provide data suggesting that the pH of 3.8 cannot be the sole reason for the local pain during REBIF injection.

Seven unselected subjects with MS, all having received REBIF 22 (22 μ g IFN- β 1a) for at least three months before our study, also participated in a skin biopsy study (reported separately). As part of the present investigation, we assessed events related to the injections. Our study was approved by the local ethics committee of the Medical Faculty at the University of Würzburg, and all patients gave written informed consent before participation.

All the recipients were asked before injection to describe their sensations during and after the procedure, to which they were all blinded. The unblinded clinical investigator made no comments until the skin biopsies had been completed the next day, nor were the participants asked any additional questions. They received 0.5 ml REBIF 22 over 10 seconds in one buttock and directly afterwards 0.5 ml placebo, or vice versa, over 10 seconds in the other buttock, by subcutaneous injection. None of the patients had previously received REBIF in the buttock. All solutions were warmed to hand temperature before injection. Injection sites were not cooled before or after injection. Steps were taken to ensure that there were no drops at the needle tips. The placebo, as provided by our local pharmacy, was of similar composition to the commercial REBIF preparation apart from IFN- β 1a and consisted, as did the placebo used in the clinical REBIF trials, of 8.0 mg/ml human serum albumin and 54.6 mg/ml mannitol, osmolality 362 mOsm/kg, pH 3.8 (adjusted with acetic acid).¹⁻³ Sterility of the preparation was extensively tested before use by a specialised commercial laboratory (Labor L+S AG, Bad Bocklet, Germany). The placebo was administered with a Sterican needle (Braun, Kronberg, Germany) of the same diameter as the REBIF needle (27 gauge).

All seven subjects reported a moderate burning pain at the REBIF site during injection. The pain was described as similar to what they had previously experienced in all cases. At the site of placebo injection, only a slight feeling of pressure during the injection was reported and almost no pain. Without specifically being asked, all seven individuals correctly identified the REBIF injection site. Our findings provide evidence

that the pain of REBIF injection cannot be solely due to the acidic pH of REBIF, because no pain was perceived with placebo injections at a similar pH. Rather, the pain may be due to IFN- β in combination with the acidic pH, to other aspects of the IFN- β formulation, or to the needle tip used for injection. Although pain can be overcome to some extent by cooling of injection site before and after the procedure, the true cause of the pain remains to be elucidated.

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M Buttman, M Goebeler, P Rieckmann

Clinical Research Unit for Multiple Sclerosis and Neuroimmunology, Department of Neurology and Department of Dermatology, Julius-Maximilians-University, Würzburg, Germany

Correspondence to: Dr M Buttman; m.buttman@mail.uni-wuerzburg.de

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Autoimmune neurological disease after cardiac surgery

A recent report on three patients who developed myasthenia gravis (MG) three to 10 weeks after cardiac surgery¹ raised the intriguing possibility that thoracotomy, by damaging the thymus, could precipitate MG. MG is an autoimmune disorder, associated with autoantibodies that bind to the acetylcholine receptor (AChR) or to muscle specific kinase (MuSK) at the neuromuscular junction. The thymus gland is clearly involved in the aetiology of some cases of MG, probably because the thymic "myoid" cells express acetylcholine receptors.² In the increasing number of older MG patients,³ however, the cause of the disease is not clear.

Voltage gated potassium channels (VGKCs) are also expressed in the thymus.⁴ Antibodies to VGKCs have recently been found in some patients with unexplained amnesia,⁵ and memory loss is common after cardiac surgery, occurring in up to 75% of patients.

For these reasons, we tested sera from 50 persons before and six weeks after cardiac surgery at St Thomas' Hospital Cardiothoracic Centre. At follow up, they were questioned regarding muscle weakness, visual disturbance or problems with memory, and swallowing difficulties. Five individuals complained of some weakness, and one

noted blurred vision. The AChR and MuSK antibodies, however, were negative in all cases. Two men (aged 49 and 57 years) had slightly raised VGKC antibody levels at follow up (107 and 118 pM, respectively, compared with less than 100 pM in healthy controls), but these levels were only slightly higher than the preoperative samples (90 and 106 pM, respectively). Neither complained of muscle weakness or memory problems.

These results do not support the hypothesis that myasthenia gravis or VGKC antibody associated amnesia are frequently precipitated, or the relevant autoantibodies induced, by cardiac surgery. However, since the thymic stroma expresses many self-antigens,⁶ and is usually damaged during thoracotomy, it would be interesting to assess the prevalence of previous cardiac surgery in patients presenting with these and other late onset autoimmune conditions.

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K Sleeman, R Rajani, J Chambers

Cardiothoracic Centre, St Thomas' Hospital, London, UK

A Vincent

Neurosciences Group, Weatherall Institute of Molecular Medicine, Oxford, UK

Correspondence to: Professor A Vincent; angela.vincent@imm.ox.ac.uk

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Development of myasthenia gravis in two patients with multiple sclerosis following interferon β treatment

We present two cases with multiple sclerosis who developed myasthenia gravis during treatment with interferon β .

Case 1

A 41 year old right-handed woman was diagnosed 3 years ago with relapsing-remitting multiple sclerosis (MS) with positive MRI findings and positive CSF for oligoclonal bands. Her neurological symptoms were long-standing, starting at the age of 20. Her family history was positive for MS, her father being a sufferer. Her past medical history was unremarkable. Since March 2001 she has been receiving interferon β and symptomatic treatment for neurogenic pain and occasional tonic muscle spasms.

On her pre-treatment assessment she demonstrated long-standing pyramidal weakness, mild ataxia, and urinary bladder symptoms such as urgency and frequency. Her disability EDSS score was 3.5. Nine months following initiation of interferon β treatment she developed progressive weakness of the neck muscles (drooping head), bilateral ptosis, intermittent double vision, and mild dysphagia. Her routine blood and biochemical tests, including thyroid function, were normal. Her electrophysiological study with repetitive stimulation was positive for myasthenia gravis. A test for acetylcholine receptor antibodies was positive at 2.2 nM/l (borderline values 0.4-1 nM/l, positive above 1 nM/l). CT of the thorax showed no thymus enlargement.

The patient was started on pyridostigmine and had a favourable clinical response.

Case 2

A 39 year old right-handed woman had a clinical history suggestive of MS from the age of 18 with recurrent episodes of sensory-motor disturbances involving her lower limbs, ataxia, and fatigue. She was diagnosed with MS at the age of 22 with positive MRI scan finding and positive CSF for oligoclonal bands. She was started on interferon β at the beginning of 2001.

On her pre-treatment assessment she demonstrated bilateral lower limb pyramidal weakness and signs, urinary bladder urgency and frequency, and chronic fatigue. Her disability EDSS score was 4.5. Approximately 12 months following the initiation of interferon β treatment she presented with progressive dysarthria, dysphagia, generalised weakness, and episodic double vision. Her routine blood and biochemical tests, including thyroid function, were normal. Her electrophysiological study with repetitive stimulation was positive for myasthenia gravis. Screening for acetylcholine receptor antibodies was positive at 1.4 nM/l (borderline values 0.4-1 nM/l, positive above 1 nM/l). CT scan of the thorax showed no thymus enlargement.

The patient was started on pyridostigmine with a favourable clinical response.

Discussion

MS is a putative autoimmune condition. The prevailing hypothesis is that autoreactive T cells of the CD4+ T helper Th₁ population orchestrate the pathogenetic process in MS.¹ Interferon β is one of the first effective immunotherapies in MS. Interferon β acts

at multiple levels, on activation of T cells,² on immune deviation in favour of Th₂,^{3,4} and on the blood-brain barrier function, and possibly exerts antiviral effects.

The development of sero-positive myasthenia gravis in our two cases during interferon β treatment may have two explanations:

- it may be a coincidental autoimmune disorder, as sporadically described in the literature⁵ or
- it may be triggered by interferon β treatment via deviation of immune response towards a predominantly Th₂ reaction.

Development of myasthenia gravis in one patient with MS during interferon- β treatment has been reported⁶ while exacerbation of myasthenia gravis has been reported in a patient receiving interferon β for chronic active hepatitis C.⁷ Of interest is the observation of induction of increased production of auto-antibodies in MS patients treated with interferon 1a and β .⁸ The longstanding history of MS in our cases with no manifestation of other autoimmune disorders would favour the suggestion of β interferon induced auto-antibodies.

J Dionisiotis

Pammakaristos General Hospital of Athens, Athens, Greece

Y Zoukos

Royal London Hospital, London, UK

T Thomaides

Pammakaristos General Hospital of Athens, Athens, Greece

Correspondence to: Dr Y Zoukos, Broomfield General Hospital, Court Road, Broomfield, Chelmsford CM1 3TL, UK; y.zoukos@btopenworld.com

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