LETTERS TO THE EDITOR

Sustained downgaze in coma after cardiac arrest

Sustained downgaze eye deviation is occasion-ally associated with lesions affecting the dorsal midbrain, usually thalamic haemorr-hage. In stuporous or comatose patients, however, this downgaze does not necessarily indicate structural pretectal damage. Sub-arachnoid haemorrhage, seizure, hepatic failure, hypoglycaemia, intoxication with sedative drugs, and hypoxic encephalopathy can cause this eye sign in comatose patients. We report on three comatose patients who showed sustained downgaze after cardiac arrest. The paper concentrates particularly on the temporal neuro-ophthalmological profile.

Between January and December 1998 we examined three patients with sustained downgaze. All three patients underwent brain CT and EEG while sustained downgaze was present (table 1). Brain MRI was performed only in patient 2, 2 weeks after admission. All patients were in a comatose state after cardiac arrest, responding only to painful stimuli. Deep tendon reflexes were slightly increased in patient 1 but normal in patients 2 and 3. Flexor plantar reflexes were elicited in all patients. Cardiac arrest was due to anaphylaxis in patient 1, cardiomyositis in patient 2, and ventricular fibrillation in patient 3. Arrest time ranged from 10 to 30 minutes before resuscitation. All patients had not received any sedative drugs.

A cardinal feature of downgaze deviation was recognised in each patient when the eyelids were raised after a period of 1 to 4 days, when the immediate post-resuscitation threat of death had subsided. Horizontal oculocephalic responses were present in all patients, and the eyes could be driven upward with vertical oculocephalic manoeuvres. The pupils were normal in size and showed normal reactions to light. In patient 1, high frequency horizontal head shaking was followed by transient conjugate upward ocular deviation. After a few seconds of horizontal head shaking at a frequency of 2 Hz, the eyes moved slowly upwards, remained there for a few seconds, and lowered slowly. This phenomenon was recognised only when sustained downgaze was evident. This upward ocular deviation could not be elicited in the other two patients. In patient 2, smooth and then saccadic ping-pong gaze was detected transiently 2 days after admission; the ping-pong gaze disappeared when the eyes began to deviate downward 4 days after admission. Marked rigidity and dorsiflexion of the neck and trunk were associated with sustained downgaze in this patient; rigidity of the limbs was mild. This abnormal rigidity and dorsiflexion resolved with the disappearance of the sustained downgaze. Muscle tonus of the other two patients was normal.

Brain CT findings in all patients and MRI findings in patient 2 seemed normal. An EEG showed a generalised delta rhythm interminned with theta waves in patient 1, low voltage fast activity in patient 2, and suppression burst in patient 3. The sustained downgaze disappeared within 1 week in all patients, but all have remained in a persistent vegetative state.

Our three patients experienced acute onset coma as a result of diffuse CNS damage after cardiac arrest. The EEG results in our patients suggested the existence of diffuse, severe brain damage. The ping-pong gaze seen in patient 2 also implied severe bilateral cerebellar damage. The sustained downgaze appeared in our patients 1 to 4 days after resuscitation. That was also the time at which patients were emerging from the most critical postevent stage. In a previously reported patient with hypoxic encephalopathy, downgaze was recognised after 2 weeks of coma. These findings suggest that sustained downgaze is not an eye sign in dying patients but that it appears in patients reaching an early recuperation stage. This notion is supported by our finding that the ping-pong gaze changed from a smooth to a saccadic pattern before appearance of the sustained downgaze in one patient; such transition suggests clinical improvement. It remained unclear which function might have improved as a prerequisite for the sustained downgaze.

Keane reported sustained upgaze deviation after cardiac arrest.1 Our present findings indicate that sustained downgaze may also be associated with hypoxic encephalopathy after cardiac arrest. The most striking difference between the sustained upgaze reported by Keane and sustained downgaze is the time of appearance; sustained upgaze appears immediately after cardiac arrest whereas sustained downgaze is recognised after a few days. The temporal relation between the upgaze or downgaze and ping-pong gaze confirms this difference as ping-pong gaze is reported to appear after resolution of sustained upgaze.2 Whereas it preceded sustained downgaze in our patient. Keane speculated that the sustained upgaze deviation after cardiac arrest resulted from hypoxic cerebellar damage due to diffuse CNS hypoperfusion.3 The possible mechanism of upgaze deviation with cerebellar damage is a disinhibition of anterior canal projections for upward vestibulo-ocular reflex caused by bilateral floccular dysfunction.4 When this has recovered, the subsiding depression of mesencephalic neuronal circuits for upgaze might explain subsequent downgaze deviation. Sustained upgaze may be a direct result of diffuse CNS hypoperfusion in which the cerebellum is severely impaired, and sustained downgaze may be a result of partial recovery from diffuse, severe cerebral depression. This is consistent with the fact that all our patients with sustained downgaze lived, although they remained in a persistent vegetative state, whereas almost all reported patients with sustained upgaze died.1

One of our patients showed transient upward eye deviation after high frequency horizontal head shaking during the period of sustained downgaze. Walker and Zee described high frequency horizontal head shaking as transiently leading to and increasing upward slow eye movement that result in downbeat nystagmus in patients with cerebel-lar degeneration. Thus, the upward eye deviation after horizontal head shaking in our patient may imply severe underlying cerebel-lar damage.

Our second patient had marked rigidity and dorsiflexion of the neck and trunk during the period of sustained downgaze. Rigidity and dorsiflexion are typical symptoms of progressive supranuclear palsy, in which the midbrain tegmentum is severely damaged.3 Bilateral lesions of the interstitial nucleus of Cajal, which lies in the midbrain tegmentum, have been reported to result in dorsiflexion of the neck similar to that seen in progressive supranuclear palsy.5 It could be that dorsal midbrain involvement was responsible for our patient’s rigidity and dorsiflexion.

More than one anatomical site or physiological mechanism may well be involved in forced downgaze in comatose patients after cardiac arrest, and the mechanistic details of this state are still unclear. However, it is important to recognize that sustained downgaze can appear transiently a few days after cardiac arrest and resuscitation.

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Table 1 Clinical data of the patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Cause of cardiac arrest</th>
<th>Arrest time (days)</th>
<th>Latent period (days)</th>
<th>Duration (days)</th>
<th>Associated sign(s)</th>
<th>EEG findings</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/68/F</td>
<td>Anaphylaxis</td>
<td>Transient upward eye deviation after head shaking</td>
<td>Delta-theta waves</td>
<td>Vegetative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/22/M</td>
<td>Cardiomyositis</td>
<td>Rigidity and dorsiflexion of the neck</td>
<td>Low voltage fast activity</td>
<td>Vegetative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/70/M</td>
<td>Ventricular fibrillation</td>
<td>Suppression burst</td>
<td>—</td>
<td>—</td>
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</table>

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Prion protein gene polymorphism and Alzheimer’s disease: one modulatory trait of cognitive decline?

Although its main biological function is still unknown, the prion protein is involved in normal synaptic function. Interestingly, the presence of a valine (V), replacing a methionine (M) at codon 129 of the prion protein gene (PRNP), has been associated with poor performance in cognitive tests in a large cohort of aged, non-demented, French people. Accordingly, this polymorphic gene represents a candidate gene for association with Alzheimer’s disease, a dementing disorder characterised by neuronal degeneration and synaptic loss. To assess whether the PRNP V/M codon129 polymorphism—alone or combined with polymorphisms in the apolipoprotein (APO)E and interleukin (IL)-1ε genes, already shown to be associated with Alzheimer’s disease—affects the occurrence or clinical features of the disease, we performed a case-control study in a cohort of Italian patients with sporadic Alzheimer’s disease and age matched healthy controls.

Venous blood was collected from 212 Italian patients (130 women, 82 men; mean (SD) age at disease onset 68.3 (8.0) years) affected by clinically probable Alzheimer’s disease, according to McKhann’s criteria. Patients were also divided into those with early disease onset (<65 years; 72 patients; mean (SD) age at disease onset 57.0 (7.5) years), and those with a late onset (>65 years; 140 patients; mean (SD) age at disease onset 73.1 (3.4) years). Blood was also collected from 201 age and ethnicity matched healthy controls (80 women, 121 men; mean (SD) age 67.2 (10.5) years), chosen among the participants in the Italian Longitudinal Study on Aging who were not affected by neurological diseases. At the time of blood collection, we recorded in all subjects a mini mental state examination (MMSE) score (score for inclusion as control subject >24/30) and—only in patients with Alzheimer’s disease—the duration of the disease.

The PRNP codon 129 M/V polymorphism was analysed by polymerase chain reaction digestion, as previously described. To overcome the paucity of VV homozygous subjects (6% in patients with Alzheimer’s disease and 10% in healthy controls, table 1), all analyses, except verification of the Hardy-Weinberg equilibrium, were focused on the combination of MV and VV (V+) compared with MM genotypes. APOE ε2–4 and IL-1ε-889 T to C polymorphisms were determined by SSCP analysis in controls (Alzheimer’s disease v healthy controls) and case-case (early onset Alzheimer’s disease v late onset Alzheimer’s disease) analyses. The relative risk for Alzheimer’s disease conferred by the carriage of PRNP V+ or MM genotypes was estimated by Cochrane-Mantel-Haenszel odds ratios (ORs). Age, sex, APOE, and IL-1ε adjusted ORs were computed by logistic regression. MMSE scores recorded in V+ and in MM carriers were compared by non-parametric rank sum test and their association with disease duration was assessed by the Spearman correlation coefficient.

The PRNP allele and genotype frequency did not differ significantly between patients with Alzheimer’s disease and controls (allele frequency: p=0.06; 3x2 genotype frequency: p=0.12). The V allele conferred a non-significant OR for Alzheimer’s disease of 0.71 (95% confidence interval [95% CI] 0.48–1.06; p=0.09; p for trend of the V allele in Alzheimer’s disease=0.04). Moreover, PRNP allele and genotype frequency were not affected by sex (p=0.18 in Alzheimer’s disease and 0.28 in controls), APOE ε4, or IL-1ε TT carrier status (data not shown).

Stratification of the Alzheimer’s disease cohort by age at disease onset showed that, although not significantly, VV genotype carriers were more represented among patients with early onset (47%) than those with late onset disease (37%), resulting in an OR for early onset disease due to the carriage of the V+ genotypes of 1.46 (95% CI 0.85–2.69, p=0.2). However, a Kaplan-Meier analysis failed to confirm this differential distribution among patients with Alzheimer’s disease, indicating that if an association existed, it was small. When we compared patients with early onset and patients with late onset disease with their respective age matched controls, we found that the V+ genotypes were associated with an OR for Alzheimer’s disease of 0.92 (95% CI 0.48–1.74; p=0.8) in the younger age group (<65 years), and of 0.63 (95% CI 0.38–1.04; p=0.07) in the older age group (>65 years; allele frequency: p=0.03, genotype frequency: p=0.04, table 1).

As expected, MMSE scores showed a negative correlation with duration of Alzheimer’s disease (r=−0.38, p=0.0001), but not with PRNP genotypes (p=0.08). Interestingly, despite a comparable education level (mean number of years in school: V+7.41, MM=7.52) and a similar mean MMSE score recorded at the time of blood collection (15.1 in V+ and 15.3 in MM), V+ carriers had a median disease duration 9 months shorter than MM carriers (38 v 47 months; p=0.038), possibly indicating a faster deterioration rate in V+ patients.

In conclusion, we failed to detect a significant association between the PRNP codon 129 polymorphism and the occurrence or clinical features of sporadic Alzheimer’s disease in Italy, irrespective of age of PRNP and IL-1ε genotype status, age, or sex. Combarros et al recently reported similar results in another southern European population of comparable size. However, our results suggest that patients with Alzheimer’s disease carrying at least one V allele might have an earlier onset of the disease and a small but significant acceleration in their cognitive decline when compared with MM carriers. This is not a surprise as, in multigenic diseases, selected characteristics of the natural history of the disease seem more prone to be influenced by gene polymorphisms than mere occurrence of disease.

In conclusion, two independent studies have now provided evidence against PRNP as a susceptibility gene for sporadic Alzheimer’s disease. Our study, however, suggests a possible modulation of disease activity due to the PRNP codon 129 polymorphism. A longitudinal assessment of a large cohort of patients with Alzheimer’s disease is needed in order to evaluate the prospective impact of the different risk factors. Further studies using prospective tests might be necessary to confirm our finding.

This work was supported in part by Telethon, Italy, by a grant from Italian MURST (40% and 60%), and by the Associazione per la Ricerca sulle Demenze (ARD). We thank Drs L. Caputo, G De Bellis, and I Biunno for caring for patients and assistance in collecting data and Mrs Liliana Zuccherelli for excellent secretarial work.

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Table 1 PRNP 129 genotype and allele frequency in patients with Alzheimer’s disease (AD) and healthy controls (HC)

<table>
<thead>
<tr>
<th>Sex</th>
<th>n</th>
<th>F</th>
<th>M</th>
<th>PRNP 129 genotypes (%)</th>
<th>PRNP 129 allele frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>212</td>
<td>130</td>
<td>82</td>
<td>126 (59)</td>
<td>73 (35)</td>
</tr>
<tr>
<td>HC</td>
<td>201</td>
<td>80</td>
<td>121</td>
<td>103 (51)</td>
<td>78 (39)</td>
</tr>
<tr>
<td>Subjects &lt;65 yrs</td>
<td>72</td>
<td>45</td>
<td>27</td>
<td>38 (53)</td>
<td>29 (40)</td>
</tr>
<tr>
<td>Subjects ≥65 yrs</td>
<td>140</td>
<td>85</td>
<td>55</td>
<td>48 (35)</td>
<td>35 (38)</td>
</tr>
</tbody>
</table>

*p=0.044, PRNP 129 V+ or MM genotype frequency in AD≥65 years compared with age matched HC.

†p=0.03, PRNP 129 V+ allele frequency in AD≥65 years compared with age matched HC.

PRNP=Prion protein gene; HC=healthy controls; F=females; M=males; AF=allele frequency; GF=genotype frequency; AD=Alzheimer’s disease.
Complex musical hallucinosis in a professional musician with a left subcortical haemorrhage

Auditory hallucinosis consists of abnormal acoustic perceptions that occur in the absence of a corresponding acoustic stimulus while the patient is aware of their non-real nature.

Musical hallucinosis represents a particular type of acoustic hallucinosis, in which the auditory perception is formed by music. It is frequent in psychiatric diseases and is sometimes reported in sensory neural deafness, but rarely after stroke.

We describe a case of musical hallucinosis in a professional musician with a left subcortical haemorrhagic lesion, presumably caused by a cavernous angioma.

A 35 year old, right handed man was referred to our inpatient department in July 1999 7 days after the onset of a slight clumsiness of his right hand followed by complex acoustic perceptions. The patient had attended a symphonic concert where an orchestral transcription of Wagner’s “Siegfried” was played: the patient is a connoisseur of music and a composer. When he returned home, about 1 hour later, his musical hallucinosis started. Auditory perceptions were described by the patient as a symphonic piece of music performed by an orchestra with numerous kettledrums and percussion instruments. It was a rather familiar music, unknown to him, but similar to what he had heard during the concert. The theme was played in a major tonality with frequent use of drums and other percussion instruments interspersed with string instruments. A chorus played by string instruments accompanied the theme. The patient said that the music resembled a piece by the late German romantic authors (for example, Mahler, Bruckner, and Wagner’s latest works). The music was initially low in intensity but progressively increased; it was reinvented in the middle of his head as if he was listening with headphones on. Conflicting emotions occurred: he felt that it was the most frightening and terrifying music he had ever heard and strongly desired to push it out of his mind but, on the other hand, he was deeply fascinated and said that he would like to compose such an exciting piece.

The patient said that during his musical hallucinosis he was able to speak, watch and understand television programs and go about his normal activities. He reported that during the phenomenon his hearing was normal and he could hear everything going on around him as if there were no noise outside the house (for example, from the road) and all the usual noise going on in his own house.

The musical hallucinosis lasted about 90 minutes and afterwards the patient fell asleep; he did not have musical hallucinosis during the next day on awakening and it did not recur during the next 20 months.

Seven days after the episode the patient was admitted to our department. On admission a neurological examination evidenced an inhibitory fibres run from the auditory cortex to lower structures of the central acoustic pathway (medial geniculate nucleus and inferior colliculus) and presumably modulate acoustic perception. The comparison of brain MRI (fig 1 A) and of a corresponding anatomical drawing (fig 1 B) suggests that the lesion just touches the acoustic radiation between the left medial geniculate body and the auditory cortex. Another explanation of such peculiar findings in our patient may derive from a recent hypothesis regarding musical hallucinosis in acquired deafness: the subcortical lesion may have caused either a disconnection between the primary auditory cortex and the association cortices or an impairment of the “neural networks for perceptions and imagery of sounds, including the auditory association and the frontal cortex.” Indeed, the closeness of the lesion to the superior temporal gyrus may interfere with the associative fibres connecting the auditory cortex to the other cerebral areas involved in musical perceptions.

Compared with previously reported cases,1 our patient presents several peculiarities. Firstly, the duration of musical hallucinosis was shorter and the auditory perceptions were heard bilaterally and not lateralised in the opposite ear. Secondly, it occurred in the absence of sensory neural deafness and might be related to a lesion involving the central acoustic pathway, even at a hemispheric level. This is not in agreement with the notion that complex hallucinosis is invariably related to damage to the peripheral acoustic pathway or to combined central and peripheral dysfunction.1 Secondly, our report greatly supports the role of the dominant hemisphere in musical processing, by contrast with the accepted notion that musical perception is a specific function of the non-dominant hemisphere.1, 14

We can speculate that the musical training of the patient might have determined the shift of musical representation from the non-dominant to the dominant hemisphere.1

Finally, several features of musical hallucinosis in our patient are fascinating. The similarity between the acoustic perceptions and the symphonic music that he had previously heard leads to the hypothesis of an involvement of acoustic memory circuits. The professional experience and the personal senstivity towards symphonic music might both have contributed in the determination of musical hallucinosis influencing the processing of musical sensations.

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Cochlear implantation in a profoundly deaf patient with MELAS syndrome

Cochlear implantation is now an established technology for restoring hearing in profoundly deaf patients. Adults who have lost all useful hearing in both ears are suitable for cochlear implantation if they are profoundly deaf (implies hearing thresholds of 100 dB nHL or worse, across the frequency range 125 to 8000 Hz), with aided hearing thresholds worse than 60 dB HL for the frequencies 250 to 4000 Hz and scoring less than 30% in a test of sentence discrimination, using their hearing aids and without lip reading. We describe a patient with MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), who was profoundly deaf and who has successfully undergone cochlear implantation and rehabilitation.

A right-handed secretary with MELAS syndrome, who was confirmed at age 22 to have an A to G transition at nucleotide 3243 in the mitochondrial genome, was referred to the cochlear implant programme of The Royal National Throat, Nose, and Ear Hospital. She had insulin dependent diabetes, congenital cataracts, short stature, leg weakness, fatigue, and hearing loss. She had never had encephalopathy or strokes. Her mother is also diabetic, has glaucoma, and has a lesser degree of deafness, and her sister has been profoundly deaf from birth. Both had slight motor retardation. The patient had begun to experience bilateral hearing loss at the age of 22, with slow deterioration up to the age of 29, by which time she was profoundly deaf in the right ear. By the age of 30 she was also profoundly deaf in the left ear and had developed tinnitus. She had no spontaneous vertigo, but sudden movements could leave her temporarily unsteady. At the age of 32, she was referred for assessment for cochlear implantation. Her ability to communicate with her family was severely restricted because of her deafness. She had developed a marked lip reading ability and was able to lip read her husband to a limited extent, but she had virtually no hearing in either ear. A CT scan of the temporal bones was normal. An MRI scan of the head showed mild temporal lobe atrophy at necropsy with associated spongy degeneration of the cortex. She had had seizures and stroke-like episodes. Her selection as a candidate for cochlear implantation was straightforward, and she has been successful in adapting to the device and has gained a significant benefit from it. The performance of the patient in the BKB word test places her in the top 5% of adult performers in our patient series. Another patient with profound deafness and MELAS, who had had seizures and strokes, has recently been reported incidentally in a larger series to have been implanted with a successful outcome, but unfortunately details were not provided.4

The fact that this patient has gained considerable benefit from her cochlear implant raises the possibility that other patients with MELAS syndrome and profound sensorineural deafness could benefit from this procedure.

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**Lead poisoning from complementary and alternative medicine in multiple sclerosis**

In response to the article “Lead poisoning from complementary and alternative medicine in multiple sclerosis,” we are very concerned that this
case has been blamed on homoeopathic plumblum metallicum that the patient used in an attempt to improve the symptoms of multiple sclerosis. The original article states that he had used a homemade remedy; this is very unlikely to have been prepared using the strict regime applied by homeopathic laboratories. A correctly prepared remedy would only contain minute traces of lead, not enough to cause toxicity.

We consider it worrying when doctors who promote modern science to find answers to often difficult questions will, when it suits, simply make assumptions without appropriate testing of the hypothesis in question.

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Anti-GQ1b IgG antibody syndrome without ophthalmoplegia: clinical and immunological features

I read with interest the review by Odaka et al1 of the range of clinical disorders manifesting anti-GQ1b IgG antibodies. Their patients were classified into Miller Fisher syndrome, Bickerstaff's brain stem encephalitis, acute ophthalmoparesis without ataxia, Guillain-Barré syndrome, and under the term “unclassified”. The last group included patients who all had external ophthalmoplegia and normal tendon reflexes, and also varying degrees of limb, facial, and bulbar weakness. I have recently encountered a patient who developed an acute, sensory polyneuropathy in association with raised anti-GQ1b IgG antibodies, whose clinical features differ from the 194 patients described in their series.

A well-preserved 35 year old man had an episode of sore throat and dry cough, with associated myalgia and fever, in May 2000. Two weeks later, he developed tingling paraesthesia first in his feet, spreading up to his knees, and then in both hands. He found it difficult to distinguish where the ground was beneath his feet because of reduced sensation. One week into this illness, he developed partial drooping of his right eyelid. He had no symptoms of weakness or double vision. On examination 3 days later, he had a partial right ptosis, but eye movements were normal and he did not report diplopia. Muscle power and tendon reflexes were normal in all four limbs. He had a rather deliberate gait because of very mild sensory ataxia with reduced sensation to pain, light touch, and vibration sensation in both legs, to the level of the knees. Joint position sense was impaired in the toes but normal in the fingers.

Nerve conduction studies 3 weeks into his neurological illness showed normal distal motor latencies, proximal conduction velocities, and F wave latencies in all four limbs. All sensory nerve action potentials were absent. Protein in CSF was raised at 0.7 g/l (acelluar sample). Conjugated IgG antibodies were raised at 1:64. Antiganglioside antibody assays showed raised IgG titres to GQ1b (1:8000), GD1b (1:11000), and GT1b (1:2200). Over the course of the next 2 weeks he improved without treatment, achieving full recovery with no residual symptoms or signs. The lack of external ophthalmoplegia and ataxia was only encountered in patients classified as Guillain-Barré syndrome in the series by Odaka et al,1 all of whom had limb weakness and reduced or absent reflexes. The electrophysiological findings in this patient were not compatible with criteria for demyelinating or axonal Guillain-Barré syndrome, but repeated studies can rarely be normal.1 Electrophysiological studies on patients with Guillain-Barré syndrome revealed external ophthalmoplegia and positive anti-GQ1b antibody titres have shown marked attenuation or absence of sensory nerve action potentials, suggesting that anti-GQ1b antibodies may be particularly involved in sensory nerve conduction failure.1

A recent report of eight cases of sensory Guillain-Barré syndrome has highlighted the existence of this variant.1 Two of these patients had normal motor nerve conduction studies, one of whom had essentially normal tendon reflexes. Not all of these patients were tested for antiganglioside antibodies. The GQ1b ganglioside is present in both sensory and motor nerves, including oculo-motor nerves,1 and the range of disease associated with anti-GQ1b antibodies could theoretically involve dysfunction in any one or more of these types of nerves in varying degrees. If the screening of antiganglioside antibodies is extended to all patients with Guillain-Barré syndrome and its variants (with or without ocular signs) in a large series, then the proportion of patients associated with anti-GQ1b antibodies will no doubt expand to include more patients without marked ataxia or external ophthalmoplegia, as in this case.

I thank Dr Hugh Willison, Southern General Hospital, Glasgow, for performing antiganglioside antibody assays, and for helpful comments.

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Odaka and Yuhi reply:

Maddison considered that clinical features of his patient were similar to those of “sensory Guillain-Barré syndrome”, as proposed by Oh et al.3 All of the patients of Oh et al had electrophysiological evidence of demyelination in at least two sensory nerves. By contrast, no evidence of demyelination in sensory nerves was shown in his patient. To produce this evidence, Maddison should have repeatedly performed sensory nerve conduction studies during the convalescent phase. Because sensory nerve action potentials were absent in his patient, the “sensory of acute sensory neuropathy” as proposed by Windelen et al may be the diagnosis.

We earlier reported a patient with a relapsing form of the acute sensory neuropathy syndrome. The patient rapidly developed marked sensory ataxia without ophthalmoplegia and limb weakness after an upper respiratory tract infection. His sensory symptoms reached their peak in a few days, followed by subsequent improvement over a few weeks. However, unsteady gait remained as a chronic deficit. Stepwise progression of his symptoms occurred over 15 years with 10 similar relapses. Sensory nerve conduction studies showed the absence of action potentials, and sural nerve biopsy showed the marked loss of small myelinated fibres. The patient’s serum had an extremely high titre of an IgM monoclonal antibody directed against b series gangliosides GD2, GD1b, GT1b, and GQ1b. His IgM reacted neither with GD3 nor with GT1a. An absorption study showed that the anti-GQ1b IgM antibody cross reacted with GD2, GD1b, and GT1b. The common sugar structure (NeuAcâ2–8 NeuAcâ2–3 [GalNAcâ1–4 Gal]â) seems to be the binding site of the IgM antibody.

Interestingly, serum IgG from the patient of Maddison reacted with GD1b, GT1b, and GQ1b, although whether his IgG had antibody activity against GD2 and GD3 was not shown. An absorption study would clarify whether his IgG reacted with a disialosyl residue linked to the intact gangliosome to b series gangliosides. An immunohistochromatic study showed localisation of GD1b in the neurons of the human dorsal ganglion. GD1b is also localised in the large neurons of the rabbit dorsal root ganglion, and Kusunoki et al.4 succeeded in the development of sensory ataxic neuropathy by sensitisation with GD1b. Autoantibody to b series gangliosides including GD1b may function in the development of acute sensory ataxic neuropathy in some patients.

Anti-GQ1b IgG antibody from patients with Miller Fisher syndrome cross reacts with GT1a. GT1a has a disialosyl residue linked to the external galactose common to GQ1b, and this may be the binding site of the IgG antibody. We investigated the fine specificity of anti-GQ1b IgG antibody in serum samples from 82 patients: 56 with Miller Fisher syndrome, 11 with Guillain-Barré syndrome, 13 with Bickerstaff’s brain stem encephalitis, and two with acute ophthalmoparesis. External ophthalmoplegia was present in all of these patients. Anti-GQ1b IgG antibodies were absorbed by GT1a in 80 (98%) of the 82 samples, by GD1b in 81 (99%), and by the other b series gangliosides GD3, GD2, or GT1b in 24 (29%). The most frequent pattern of fine specificity was the cross reaction with GT1a alone, seen in 56 (68%) samples. By contrast, we recently noted that some patients with the “ataxic form of Guillain-Barré syndrome” showed no or minimal external ophthalmoplegia but had anti-GQ1b IgG antibody. Anti-GQ1b IgG antibody from the patients, as well as those with Miller Fisher syndrome, were absorbed by GT1a. The finding that ataxic Guillain-Barré syndrome and Miller Fisher syndrome have in common an autoantibody with the same fine specificity over a continuous range. We should not have used...
the term “anti-GQ1b IgG antibody syn-
drome”, but rather, “anti-GQ1b GT1a IgG
antibody syndrome”, which includes Miller
Fisher syndrome, Guillain–Barré syndrome
with ophthalmoplegia, Bickerstaff’s brain
stem encephalitis, acute ophthalmoparesis
without ataxia, and the ataxic form of
Guillain–Barré syndrome. Madsdon did not
show that his patient’s IgG had antibody
activity against GT1a, but his case could be
categorized as the syndrome of acute sensory
neuropathy if the patient’s IgG did not react
with GT1a.

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1 Oh SJ, LaGanke C, Clausen GC. Sensory
2 Winderbank AJ, Bleier MD, Dyck PJ, et al. The
syndrome of acute sensory neuropathy: clinical
features and electrophysiologic and pathologic
sensory neuropathy associated with IgM anti-
body against B-series gangliosides containing a
Galα1-3Galβ1-4GlcNAc2 residue (G1a configuration).
4 Sasaki K, Yuki N, Hizata K. Features of sensory
atonic neuropathy associated with anti-GD1b
sensory neuropathy induced by sensitization with

BOOK REVIEWS


This book is written in three parts for medical professionals requiring an introduction to critical appraisal of medical information. The first examines the “justification and validity of medical information”, providing “definitions and relevant topics of statistics and epidemiology”. The second is devoted to “complementary aspects of systematic critical appraisal of medical information”. The third part “presents some statistical techniques that are commonly used in published articles”.

It would have been helpful if the reader had been provided with references for the topics discussed and those not pursued. The list of books and published papers given near the end of the book are never referred to in the text. Whereas the Normal and binomial distributions are discussed, no other distributions are covered, in particular the Poisson distribution.

Some readers may find the first few chapters heavy going, but they are worth persevering with. The author should have said that the use of the correlation coefficient for indicating agreement between one test and a gold standard is misleading (see Bland JM and Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet, 1986, 307–10).

In the discussion on confidence intervals, the author should have used the phrase “likely to lie” rather than “assumed to lie”. It should have been stated that the relative risk is not appropriate for case-control studies. The terms “multivariable” and “multivariate” are used incorrectly at various places in the text. It should have been made clear that a correlation of zero does not necessarily imply independence.

There are some typographical errors. In particular, in chapter 25, it is the independent variables that are categorical. The book is clearly written and the subject matter logically developed. It is well suited to its target audience and would be a useful addition to any clinician’s bookshelf.

NEVILLE VERLANDER


Several large scale textbooks cover much of the same ground as this fairly modest, 300 page volume. It is questionable whether the information it contains would be adequate for someone practising or training as a specialist neuroradiologist and, indeed, the preface indicates that it is aimed at general radiologists and those in training, rather than subspecialists. It might be suitable for neuro-
science trainees. However, given that, the readers’ needs deriving substantially from those of the subspecialist, who will already have a grounding in the subject. What does it offer the generalist who has to report on CT and MRI studies?

Part 1 contains two 20 page atlases, one of normal anatomy as displayed by MRI and CT, and another of brain (actually intracra-
nial) pathology. The former contains a sufficient number of types: “mammillary body”, “thalamic (both normal and abnormal), “tubercu-
lum sella”, “gyrus rectus” to confuse the uninitiated, plus terms recognised in “radiology anatomy” but not found in anatomists’ texts, such as “tical” and “suprassellar” cisterns. This presents problems for generalists hoping to hone their neuroradiological skills. What do they require, but will not find here, are extensive examples of confusing normal variants, artefactual abnormalities, and things which resemble others the management of which is radically different. In this respect, the implied message on page 38, for example, that extensive parenchymal calcification on CT usually indicates metabolic disease (and should presumably prompt further investigation) is not overly helpful.

In Part 2, eight chapters, each with about 20 pages and 30 illustrations, deal with the usual topics: traumatic and congenital abnormalities, infections and inflammatory diseases, etc, and two shorter ones cover hydrocephalus and “advanced techniques in neuroradiol-
ye”. The last has, I think, no part in such a book. Most of the chapters are in general well prepared and the standard of the illustrations is high; frank errors are relatively rare. Given the British provenance of the book I was, as usual, distressed by the arguably excessive reliance of almost all the contributors on the transatlantic literature. Some chapters are heavily, others sparsely referenced; the index is reasonably full.

IVAN MOSELEY