movements were broken but there was no nystagmus. Speech was not dysarthric and the remainder of the cranial nerve examination was normal. There was evidence of left finger–nose incoordination. Lower limb reflexes were absent. Plantar responses were flexor. Gait was wide based and tandem gait was markedly impaired.

Investigations

Cranial MRI (fig 1) on admission revealed swelling of the cerebellum with distortion of the fourth ventricle and extensive signal change within the cerebellar hemispheres, particularly on the left. There was moderate obstructive hydrocephalus. The venous sinuses were patent. There was evidence of minor, chronic, hemispheric deep white matter signal change. There was renal impairment (creatinine 171 µmol/l) and heavy proteinuria. Transthoracic echocardiogram revealed moderate left ventricular hypertrophy. Subsequent investigations excluded secondary causes of hypertension such as hyperaldosteronism, renal artery stenosis or pheochromocytoma. Autonomic function tests, including a tilt table study, revealed no evidence of cardiovascular autonomic failure.

The severe hypertension was treated initially with recurrent oral doses of a calcium channel blocker (modified release nifedipine) titrated against blood pressure. Gradual reduction of blood pressure within the first 12 h was matched by significant clinical improvement: he felt much better, nausea and vertigo settled, and the eye movement abnormalities and ataxia resolved. His renal impairment and proteinuria improved within days. Repeat cranial MRI 5 days after admission (fig 1) showed almost complete resolution of the cerebellar abnormalities and hydrocephalus. Sustained blood pressure control was achieved using a combination of a long acting angiotensin converting enzyme inhibitor, a calcium channel blocker and a beta blocker.

Discussion

Although cerebellar involvement is reported in HTE,^{1,2} it very rarely occurs in isolation and leads to secondary obstructive hydrocephalus.^{3,4} Several cases with predominant brainstem involvement and resultant hydrocephalus have been reported.^{5,6} Neurological signs in HTE are not usually focal, and in the rare reported cases in which isolated cerebellar involvement with hydrocephalus was noted, presentation tended to be dramatic with obtundation.^{3,4} Our patient presented without encephalopathy but with episodic vertigo, nausea and ataxia consistent with more focal cerebellar or vestibular dysfunction. Only one previously reported case occurred in an individual without a documented history of long-standing poorly controlled hypertension, renal failure or diabetes mellitus.³ Our patient had no known significant past medical history, although given the presence of left ventricular hypertrophy and the minor, chronic, white matter changes in the cerebral hemispheres, it is probable that he had unrecognised hypertension for some time. In view of the absence of evidence of more generalised autonomic dysfunction, it is unlikely that the history of Holmes–Adie syndrome is relevant to the current clinical presentation.

In addition to prompt treatment of hypertension, neurosurgical intervention and CSF diversion to relieve obstructive hydrocephalus

was necessary in the cases with isolated cerebellar involvement reported previously.^{3,4} Ventriculostomy placement in those cases did not result in lowering of blood pressure, indicating that hypertension was not secondary to raised intracranial pressure.³ In our patient, prompt but controlled lowering of blood pressure alone led to rapid clinical improvement and resolution of the cerebellar oedema and hydrocephalus. In those rare cases without encephalopathic features or a rapidly deteriorating neurological state, the need for ventricular drainage may be obviated by institution of medical therapy.⁶ Awareness of this rare reversible cause of obstructive hydrocephalus is important for both neurologists and neurosurgeons.

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Peripheral neuropathy in chromosome16q22.1 linked autosomal dominant cerebellar ataxia

Autosomal dominant cerebellar ataxia (ADCA) includes heterogeneous neurodegenerative diseases with or without various neurological signs and symptoms. Ishikawa *et al* reported a new type of ADCA, named chromosome16q22.1 linked ADCA (16q-ADCA), attributed to a heterozygous C→T substitution in the 5′ non-coding region of *puratrophin-1* gene.¹ We searched

for this mutation in 168 patients from 129 families with ADCA and found it in six patients. The patients generally showed late onset pure cerebellar ataxia similar to previous reports² but two had mild axonal neuropathy and orthostatic hypotension (OH). Our results suggest that 16q-ADCA shows a broader clinical presentation than previously thought.

Case report

Patient No 1

An 81-year-old Japanese woman had dysarthria at 52 years of age, unsteady gait at 56 years, limb ataxia at 76 years and severe truncal ataxia, requiring a wheelchair. Her family history included progressive ataxia in her older sister, younger brother and son. She had cervical spondylosis at the C3–C7 level. Ocular movement was almost normal. The score on the International Cooperating Ataxia Rating Scale³ (ICARS) was 66/100. Deep tendon reflexes (DTRs) were increased, with extensor plantar reflexes. Sensation of pain was almost normal, while vibratory sensation was moderately disturbed in the lower limbs. Passive head up tilt testing (HUT) performed at 60° for 30 min revealed OH, with a slightly increased pulse rate (table 1).

Patient No 2

A 58-year-old man, the son of patient No 1, had dysarthria and imbalance at 52 years of age. He had no cervical spondylosis. At 58 years he had scanning speech, normal ranges of ocular movement with gaze evoked nystagmus, and mild limb and truncal ataxia. The ICARS score was 25/100. DTRs were normal, without abnormal plantar reflexes. Pain sensation was almost normal, while vibratory sensation was mildly disturbed in the lower limbs. The autonomic system was nearly normal, except for OH (table 1).

Genetic analysis was performed after obtaining patient informed consent. The results ruled out spinocerebellar ataxia (SCA) types 1, 2, 3, 6, 7, 8, 12 and 17, as well as dentatorubral pallidoluysian atrophy. PCR amplification and *Eco*NI restriction fragment length polymorphism or sequence analyses of the *puratrophin-1* gene revealed a heterozygous C→T substitution at 16 nt upstream of the putative translational initiation site,¹ as found in four of the 168 patients from the 129 families with ADCA. We analysed 10 microsatellite markers around the *puratrophin-1* gene (*GGAA05*, *GGAA10*, *GATA01*, *D16S421*, *TA001*, *CATG003*, *17msm*, *CTTT01* and *D16S3095*) using an ABI 3100-Avant genetic analyser (Applied Biosystems, Foster City, California, USA).¹ All patients shared a haplotype “1-3-2-3-1-4-2” for markers 16cen-*GGAA05*-*GGAA10*-*GATA01*-*D16S421*-*TA001*-*CATG003*-*17msm*-16qter, which matched a reported founder haplotype between *GATA01* and *17msm*.¹ This finding suggested that 16q-ADCA shows a strong founder effect and that our atypical cases have similar genetic backgrounds. Brain MRI showed atrophy of the cerebellum, but not of the brainstem, in patient Nos 1 and 2. The results of electrophysiological tests, tilt tests and ¹²³I-meta-iodobenzylguanidine myocardial scintigraphy (¹²³I-MIBG-scintigraphy) are summarised in table 1. Audiograms were almost normal. Needle EMG revealed increased amplitude and prolonged duration of motor units without increased spontaneous activities in the tibialis anterior or extensor hallucis longus muscles. Neither patient had systemic diseases or conditions,

Table 1 Data from nerve conduction study and test of autonomic nervous system in the two patients

			Normal range	
	Patient No 1 (81 y)	Patient No 2 (52 y)	Elderly	Non-elderly
Nerve conduction study				
Rt median nerve				
Distal latency (ms)	3.28	3.95	2.3–3.9	2.2–3.8
MCV(m/s)/CMAP(mV)	50.8*/6.1*	55.7/6.9*	51.2–64.9/7.2–20.3	51.6–65.8/7.8–23.9
SCV(m/s)/SNAP(μV)	49.9*/4.8	54.5/3.6	50.0–64.4/0.1–22.0	51.4–68.5/2.3–25.1
Rt ulnar nerve				
Distal latency (ms)	2.50	2.45	1.8–3.0	1.8–2.8
MCV(m/s)/CMAP(mV)	55.6/11.9	55.7/2.0*	52.9–66.9/8.6–20.0	53.0–68.3/9.9–21.2
SCV(m/s)/SNAP(μV)	50.6*/3.5	57.8/7.8	51.3–68.0/0.4–15.5	53.0–69.7/1.0–19.8
Rt tibial nerve				
Distal latency (ms)	4.02	3.10	2.6–4.7	2.2–4.1
MCV(m/s)/CMAP(mV)	44.8/15.1	46.1/1.0*	41.2–54.2/2.7–28.3	43.0–57.0/7.2–31.8
Rt sural nerve				
SCV(m/s)/SNAP(μV)	52.2/4.3	60.1/4.4	41.1–57.0/0.1–18.2	41.9–57.5/2.0–24.4
Short sensory evoked potential				
N19 (ms)	Not evoked	Not evoked	18.2–24.5	17.8–23.9
P36 (ms)	43.4*	40.5	35.2–43.2	34.5–42.5
Head up tilt test				
BP (mm Hg)	152/89→129/66	146/84→126/68		
PR (/min)	72→89	81→77		
ΔAVP (pg/ml)	1.3	2.4		>0.46 †
ΔA (pg/ml)	38	51		>22 †
ΔPRA (ng/ml)	6.4	1.3		>1.0 †
CV-RR (%)	3.43	3.57	>1.30	>3.43
QTc intervals				
Max (ms)	512*	408		370.1–466.1
Min (ms)	449*	390		357.3–426.1
Mean (ms)	485*	390		360.2–449.4
QTc dispersion (ms)	63*	18		17.5–34.5
¹²³ I-MIBG myocardial scintigraphy				
Initial H/M ratio	1.92*	2.13		2.02–2.57
Delayed H/M ratio	1.69*	2.3		1.96–2.63
H/M washout ratio (%)	47.3*	33.0		18.8–41.5

ΔA, increase in plasma adrenaline activity; ΔAVP, increase in plasma arginine-vasopressin concentration; BP, blood pressure; CMAP, compound motor action potential; CV-RR, coefficient variation of RR interval; H/M, heart/mediastinum; MCV, motor conduction velocity; ¹²³I-MIBG, ¹²³I-meta-iodobenzylguanidine; PR, pulse rate (beats/minutes); ΔPRA, increase in plasma renin activity; Rt, right side; SCV, sensory conduction velocity; SNAP, sensory nerve action potential; QTc, rate corrected QT.

Normal range of nerve conduction study was calculated statistically at Nara Medical University (mean (2 SD)).

Non-elderly, measured in non-elderly controls (46.9 (12.7) years old, n = 105). Elderly, measured in elderly patient controls (69.5 (7.8) years old, n = 107).

Normal values of CV-RR were above $-0.066 \times \text{age} + 6.840$.

Normal ranges of H/M ratio (initial, delayed and washout) on ¹²³I-MIBG myocardial scintigraphy were calculated statistically at Nara Medical University (Shimazu Prism 2000XP).

*Abnormal value.

†The normal value was described in a previous report (Deguchi *et al.* *JNS* 2004;75:110–115).

including diabetes mellitus, malnutrition, ischaemic heart disease or collagen disease. They were receiving no medications with potential effects on the autonomic nervous system.

Discussion

The results of nerve conduction studies (NCS) in patient Nos 1 and 2 revealed reduced compound muscle action potentials (CMAPs) with slightly or mildly decreased nerve conduction velocities, indicating axonal sensorimotor neuropathy.⁴ Because aging can affect the outcome of NCS, the results for patient No 1 (81 years) were compared with those for 107 elderly controls (table 1). Needle EMG findings were consistent with involvement of peripheral motor nerves. Clinically, our patients had normal pain sensation but disturbed vibratory sensation, suggesting large fibre dominant axonal neuropathy. Delayed cortical potential with unevoked potential in the lumbar region on short sensory evoked potentials (SSEP) together with normal distal sensory nerve velocities in patient No 1 suggested involvement of proximal peripheral nerves. Alternatively, sensory systems might have been centrally affected. Three of the other four

patients with 16q-ADCA showed decreased DTRs in four limbs, which may reflect peripheral neuropathy, while patient No 1 had increased DTRs with extensor plantar reflexes. These pyramidal signs as well as abnormal SSEP may be ascribed to her severe cervical spondylotic myelopathy rather than 16q-ADCA, as they were absent in patient No 2, the son of patient No 1. However, we cannot rule out that such central sensorimotor involvement might have developed over a longer duration of 16q-ADCA in patient No 1. In addition to polyneuropathy, patient Nos 1 and 2 had OH. On HUT, increased plasma arginine-vasopressin concentrations and renin activity suggested that their OH was not due to involvement of the central autonomic nervous system. In patient No 1, abnormal QTc intervals and dispersion suggested involvement of the cardiac post-ganglionic sympathetic nervous system, which was supported by the abnormal findings of ¹²³I-MIBG-scintigraphy. Unfortunately, the other four patients with 16q-ADCA did not return to our hospital to undergo NCS or tests for OH because of severe disability. Our findings are inconsistent with those reported for 16q-ADCA, but agree with

those found in many other types of ADCA. Van de Warrenburg *et al* reported a high prevalence (70.4%) of peripheral nerve involvement in patients with SCA1, 2, 3, 6 and 7.⁴ Sensory or sensorimotor axonal neuropathy is also associated with other types of ADCA, including SCA14.⁵ OH is found in SCA1 and SCA3.³ Collectively, available evidence suggests that 16q-ADCA may also involve nervous systems unrelated to the cerebellum, although only small numbers of patients have been studied.

In summary, we demonstrated that 16q-ADCA can be associated with peripheral neuropathy and OH, extending the clinical presentation of this disease. A previous study reported that SCA4, an ataxia closely linked to a nearby locus to the one affected in 16q-ADCA, is clinically distinct from the latter disease because of the presence of sensory axonal neuropathy and pyramidal signs.¹ However, our findings may suggest that SCA4 and 16q-ADCA are allelic. Further clinical studies and genetic analyses may help to establish these diseases as new clinical entities.

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Recurrent herpes simplex virus encephalitis secondary to carbamazepine induced hypogammaglobulinaemia

Herpes simplex encephalitis (HSE) is frequently complicated by seizures. Immunosuppression is a recognised side effect of anticonvulsant therapy. We present a case of recurrent HSE where host immunocompetence was impaired because of hypogammaglobulinaemia, most likely induced by carbamazepine therapy.

A 40-year-old man presented to his local hospital with a 5 day history of rigors, nausea, vomiting and photophobia. He reported formed visual hallucinations and his wife complained that over the preceding week he had been uncharacteristically short tempered. A tonic-clonic seizure was witnessed in the accident and emergency department. A cranial CT scan was normal. CSF analysis showed 120 white cells/mm³ (lymphocytes 100%), 3 red cells/mm³ and no organisms on gram stain. The CSF opening pressure was 36 cm water and protein concentration 770 mg/l (150–450). He was treated with intravenous cefotaxime, aciclovir (10 mg/kg) and phenytoin, with a presumptive diagnosis of encephalitis. Increased signal in the right medial temporal lobe was noted on an MRI scan. An EEG revealed abnormal excess theta/delta waves over both hemispheres, consistent with diffuse cerebral dysfunction. Dexamethasone (4 mg three times daily) was started on day 2 of

admission. Subsequently, herpes simplex virus (HSV) DNA type 1 was detected by PCR analysis of CSF. Serum immunoglobulin levels were normal: IgA 2.47 g/l (1.0–5.0), IgG 12.5 g/l (6.8–15.6) and IgM 0.74 g/l (0.5–2.8), as was serum electrophoresis. He completed 3 weeks of intravenous aciclovir therapy and was discharged on oral phenytoin.

One month after discharge, he re-presented with a maculopapular rash and mouth ulcers. A skin biopsy confirmed erythema multiforme and carbamazepine was substituted for phenytoin.

Seven months after his initial presentation, he was admitted to our hospital following a tonic-clonic seizure. His wife reported that he had been increasingly agitated over the preceding 10 days. He was pyrexial, confused and non-compliant with anticonvulsant drug therapy. A cranial CT scan demonstrated atrophic changes in the right temporal lobe. The CSF opening pressure was 38 cm water, white cell count 20 cells/mm³ (82% lymphocytes, 18% polymorphs), protein concentration 600 mg/l and glucose 3.9 mmol/l (blood glucose 7.9 mmol/l). He was restarted on intravenous aciclovir (10 mg/kg) and cefotaxime. An MRI scan confirmed an area of scarring in the right medial temporal lobe. EEG findings were consistent with viral encephalitis. Immunoglobulin levels revealed profound hypogammaglobulinaemia; IgA 0.85 g/l (0.8–2.8), IgG 1.1 g/l (6–16) and IgM 0.16 g/l (0.5–1.9). (The immunoglobulin reference ranges vary between the two hospitals.) A full blood count demonstrated lymphopenia; total lymphocyte count 0.9×10⁹/l. Lymphocyte subsets were normal on immunophenotyping. CSF PCR detected the presence of HSV DNA type 1.

Hypogammaglobulinaemia was attributed to carbamazepine therapy; this was cautiously withdrawn and substituted with sodium valproate. Antibiotic prophylaxis and twice weekly intravenous pooled human immunoglobulin replacement therapy (Flebogamma 0.4 g/kg) (IVIg) were commenced. He completed 3 weeks of intravenous aciclovir therapy (10 mg/kg). Regular immunoglobulin was continued for 6 months. The IgM level was monitored during this time as a marker of immune recovery (IVIg contains negligible levels of IgA and IgM). Immunoglobulin levels were normal 6 weeks after starting IVIg therapy (IgA 1.29 g/l, IgG 11.0 g/l and IgM 0.39 g/l). However, after 8 months (when IVIg replacement had been discontinued), immunoglobulin levels fell again (IgG 3.6 g/l, IgM 0.32 g/l with normal IgA) and he received two further infusions of IVIg (0.4 g/kg) over a 6 month period. It is now 9 months since he was last treated with IVIg and his immunoglobulin levels remain normal off treatment (IgG 7.05 g/l). No alternative cause for hypogammaglobulinaemia has since emerged. He has been seizure free for 2 years. Psychometric testing highlights difficulty with tasks requiring complex attention skills and significant anterograde memory impairment. He has returned to part-time employment.

The incidence of recurrent HSE following aciclovir therapy has been reported as up to 5%.¹ Low levels of antibody generally predispose to extracellular bacterial infection but susceptibility to viral infection,² including enteroviral meningo-encephalitis, is recognised.

Anticonvulsants have been reported to cause immunosuppression, typically IgA deficiency, although carbamazepine has also been

associated with low levels of IgG.^{3–5} There are insufficient data to be sure of the mechanism underlying hypogammaglobulinaemia induced by carbamazepine, but the majority of the few reported cases cite low levels of circulating B cells with normal cell mediated immunity.^{3–5,6} Fortunately, immunosuppression attributed to anticonvulsants is generally reversible following drug withdrawal.

The true prevalence of immunosuppression secondary to anticonvulsant therapy is difficult to estimate. One study reported that 60% of general hospital patients on phenytoin and 47% of those on carbamazepine fail to mount delayed hypersensitivity reactions to antigens or make antibodies to *Salmonella typhi* and tetanus toxoid.⁴ Both visceral leishmaniasis⁶ and reactivation of human herpes virus 6⁷ have been reported in patients with hypogammaglobulinaemia secondary to carbamazepine therapy but, to our knowledge, recurrent HSE has not been previously attributed to anticonvulsants.

Erythema multiforme is a recognised side effect of phenytoin,⁸ thought to be the causative agent in this case. However, erythema multiforme is associated with HSV⁹ and recurrent erythema multiforme with hypogammaglobulinaemia has also been reported.¹⁰ Other clinical signs of HSE and immunoglobulin levels were not recorded when this patient presented with erythema multiforme.

Given that seizure activity is a frequent complication of encephalitis and that many of these patients require long term anticonvulsant treatment, our finding of recurrent HSE associated with hypogammaglobulinaemia due to carbamazepine has treatment and monitoring implications. It may be prudent to consider monitoring for hypogammaglobulinaemia in these patients for whom viral reactivation can have such potentially disastrous consequences. In the absence of routine monitoring, recurrent viral or bacterial infection certainly necessitates measurement of immunoglobulin levels.

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