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IgG Anti-GT1a antibodies which do not cross react with GQ1b ganglioside in a pharyngeal-cervical-brachial variant of Guillain-Barré syndrome

IgG anti-GT1a antibody which cross reacts with GQ1b ganglioside is associated with ophthalmoplegia in Guillain-Barré syndrome and in Fisher's syndrome, a variant of Guillain-Barré syndrome.¹ Pharyngeal-cervical-brachial weakness is another regional variant of Guillain-Barré syndrome originally described by Ropper.² Its symptoms resemble those of botulism and diphtheria and are characterised by marked oropharyngeal, neck, and shoulder weakness with areflexia only in the arms. We report on a patient with this variant who had high titres of serum IgG anti-GT1a antibody which did not cross react with GQ1b.

A 55 year-old woman was admitted due to sudden onset ptosis, trouble with swallowing, and nausea and vomiting. One week before admission she had had an upper respiratory infection with diarrhoea which lasted for several days. On admission, dilated pupils and ocular paralysis were noted. Fever of up to 40°C lasted for a week. Her neurological symptoms were at their worst on day 5. At that time, she was alert but could not open or move her eyes or swallow anything. Her pupils were dilated with sluggish light reflexes. The tip of her tongue did not protrude from her mouth. The Medical Research Council grades for the facial muscles ranged from 3 to 4; neck flexion and extension were graded 2; the deltoid and the biceps brachii and triceps muscles 4. Muscle strength in the lower limbs was normal. Deep tendon reflexes were absent in all the limbs, and the Babinski sign was negative. There was no sensory disturbance or cerebellar ataxia. She complained of headache, nausea, and vertigo on turning her head, but no meningeal signs were present. Her white blood cell count (15 600/ μ l) and serum C-reactive protein (9.0 mg/dl) were raised. Routine laboratory findings for liver and renal functions were normal. On day 5 her CSF had a raised protein concentration of 80 mg/dl, and

cells were 7/ μ l. Motor conduction velocity in the right tibial nerve on Day 11 was slightly reduced (37 m/s), whereas the motor and sensory conduction velocities in the right medial nerve were normal. A stool culture was negative for *Campylobacter jejuni*. Botulism and diphtheria were excluded because her neurological symptoms occurred a week after the onset of diarrhoea. Results of the nerve conduction and CSF studies showed abnormal values. Guillain-Barré syndrome was diagnosed. A daily intramuscular injection (8 mg/day) of dexamethasone was given for 3 days then tapered off over the next 20 days. Two weeks after admission, her internal ophthalmoplegia and dysphagia had disappeared. One month later, ocular movements were almost normal, ptosis remained only in the right eye, the strength of the neck muscles had increased to 4, and deep reflexes became detectable. All these symptoms disappeared within 3 months of onset.

Serum antiganglioside antibody titres were determined using an enzyme linked immunosorbent assay (ELISA). On day 11, the titres of anti-GM1, GM2, GD1a, GD1b IgG, and IgM antibodies were <500; whereas the titre of the IgG anti-GT1a antibody had increased to 16 000 and that of the anti-GQ1b antibody was 500 (normal ranges were set at <500). No IgM antibodies to GT1a or GQ1b were detected. Thin layer chromatography with immunostaining confirmed that her serum IgG reacted with GT1a but not with GQ1b or GD1a (figure). An absorption study showed that her IgG anti-GT1a antibodies were not absorbed by GQ1b, GD1a, or GM1 (data not shown). Three months after onset, the respective serum titres of the anti-GT1a and anti-GQ1b IgG antibodies had decreased to 500 and <500.

The regional distribution of her symptoms was the same as that of the pharyngeal-cervical-brachial variant of Guillain-Barré syndrome, except for the areflexia of the legs. Based on clinical observations of three patients, Ropper² described this variant as sparing the power and reflexes in the legs. One of his patients, however, had generalised areflexia. We therefore classified our patient as having the pharyngeal-cervical-brachial variant of Guillain-Barré syndrome. Her headaches, nausea, and vertigo suggest the involvement of a central component.

Serum antiganglioside antibodies are present in patients with Guillain-Barré syndrome. Some of these antibodies are associated with certain clinical variants or signs of this syndrome. Chiba *et al.*¹ detected IgG anti-GT1a and anti-GQ1b antibodies in most of a group of patients with Fisher's syndrome or

Guillain-Barré syndrome with ophthalmoplegia and showed that the anti-GT1a antibodies in these patients cross reacted with GQ1b. Our patient with the pharyngeal-cervical-brachial variant of Guillain-Barré syndrome also had increases in IgG anti-GQ1b and anti-GT1a antibodies that paralleled the clinical course. The anti-GT1a antibody titre in our patient, however, was much higher than the anti-GQ1b antibody titre; moreover, the anti-GT1a antibody did not cross react with GQ1b. Mizoguchi *et al.*³ also detected IgG anti-GT1a antibodies which did not cross react with GQ1b, as well as anti-GD1a antibodies in the serum of a patient with this Guillain-Barré syndrome variant. Furthermore, O'Leary *et al.*⁴ reported IgG anti-GT1a and anti-GQ1b antibodies in three patients with acute oropharyngeal palsy. The presence of IgG anti-GT1a antibodies in these patients and in ours was associated with the emergence of acute polyneuropathy with marked lower cranial nerve involvement. IgG anti-GT1a antibodies which do not cross react with GQ1b may be closely related to the proclivity of Guillain-Barré syndrome to manifest oropharyngeal palsy or to the cause of its pharyngeal-cervical-brachial variant. The IgG anti-GT1a antibody present in Fisher's syndrome may recognise a structure common to GT1a and GQ1b gangliosides,¹ whereas in the pharyngeal-cervical-brachial variant it would react with another epitope specific to GT1a.

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Dexamethasone is not necessarily unsafe in primary supratentorial intracerebral haemorrhage

Controversy surrounds the role of steroids in the treatment of intracerebral haemorrhage.¹ Theoretically, the short term use of dexamethasone is justified because it lessens the damaging effects of cerebral oedema, decreases intracranial pressure, and strengthens the blood-brain barrier. However, the possible benefit has to be weighed against the risk of complications, especially infections and gastrointestinal haemorrhage.²

Thin layer chromatography with immunostaining. Thin layer chromatography plates stained with (A) orcinol/sulphuric acid for hexose; (B) IgG from our patient, subsequently stained by peroxidase conjugated antihuman IgG antibodies; (C) IgG from a patient with Bickerstaff's brain stem encephalitis. Lane 1: bovine brain ganglioside mixtures. Lane 2: the GD1a and GT1a fraction separated from bovine brain ganglioside mixtures by Q-sepharose column chromatography. Lane 3: fraction enriched with GT1a and GQ1b. The plates were developed with C-M-0.2% calcium chloride in water (5:4:1 by volume).

So far, only two randomised, controlled trials concerning this controversy have been reported. One trial of 40 patients assumed to have intracerebral haemorrhage, found no beneficial effects of steroids.³ However, this study had 22 patients with haemorrhagic infarcts or posterior fossa haemorrhage, and the outcome measures used had little clinical relevance regarding functional ability of the patients. The other trial, from Thailand,⁴ was well designed, but had to be terminated prematurely after an interim analysis disclosed lack of benefit and presence of clinically important adverse effects. Patients in the dexamethasone group had more frequent infections, gastrointestinal haemorrhage, and diabetogenic effect, than the placebo group. There was a possible longer early survival in a subgroup with less severe stroke. Good recovery was noted in 17% of patients in the dexamethasone group, compared with 10% of patients in the placebo group, giving a difference of 7% in favour of the dexamethasone group.

In our experience, the complication rates are not as high with dexamethasone as reported by Pongvarin *et al.*⁴ To consider the issue of safety of dexamethasone in primary supratentorial intracerebral haemorrhage, we undertook a double blind, randomised, placebo controlled trial as a pilot project.

Twenty six patients in the age group 40–80 years, with primary supratentorial intracerebral haemorrhage confirmed by brain CT, presenting within 5 days of onset were included. Patients with a history of previous disabling stroke or contraindications to steroid treatment were excluded. Informed consent was taken from relatives of all patients before admission into the trial. Dexamethasone was given intravenously, at a dose of 4 mg 6 hourly for 12 days, followed by 4 mg 12 hourly for two days and 2 mg 12 hourly for 2 days. Placebo injections of saline were given in the same dosage, from ampoules of similar size and shape, and with comparable labels, filled with a colourless solution indistinguishable from dexamethasone. No one involved with the study knew whether a particular patient was receiving dexamethasone or placebo. All patients received injectable ranitidine, 50 mg 8 hourly, for the period of the trial. The remainder of patient care was specified by their attending neurologist. The allocated treatment was stopped if the attending neurologist thought that the patients had developed a complication likely to be caused by, or aggravated with dexamethasone. No other antioedema measure (mannitol/glycerol) or neurosurgical intervention was undertaken, except in one patient who was found to have a ruptured anterior communicating artery aneurysm, diagnosed after randomisation.

Details of history and physical examination conducted at the time of admission were recorded. Haematoma size was calculated using the formula given by Kothari *et al.*⁵ Outcome measures of all patients were assessed by one of us (PD), using the Glasgow outcome scores⁶ at day 7 and at discharge. Fasting blood sugar was done one week after starting the treatment, to detect any diabetogenic effect. The development of fever after entry into the study was considered to be indicative of infection, irrespective of whether the focus of infection was detected or not. Statistical methods used were χ^2 test with continuity correction for categorical variables and a two tailed *t* test for continuous data.

The clinical characteristics, complications, and outcome of the patients are shown in the table. Both groups were well matched for age, hours from haemorrhage to treatment, blood pressure, volume and location of haematoma, and presence of intraventricular extension of blood. However, there were more comatose patients (Glasgow coma scale score <7) in the dexamethasone group (5/12) than in the placebo group (3/14).

The complication rates were higher in the placebo group than in the dexamethasone group (placebo group, 10 *v* dexamethasone group, 4), but the difference was non-significant. One patient in each group was found to be non-eligible after randomisation, and their allocated treatment was stopped within 3 days, but they continued to remain in the allocated group for analysis.

In all, seven patients died (five patients in the dexamethasone group died due to herniation within the first week and two patients in the placebo group died; one died of herniation in the first week, and the other died due to septicaemia on day 36). There was no difference between the groups in the number of patients who had a good outcome (2/12 in the dexamethasone group *v* 2/14 in the placebo group).

There could be many reasons why Pongvarin *et al.*⁴ found a higher frequency of adverse effects due to dexamethasone. Firstly, it may have been a chance finding. If they had continued the study further, the placebo group may have had similar complications such as infections or hyperglycaemia, thereby making the difference between the two groups non-significant. Secondly, the dexamethasone group may have had a higher proportion of serious patients who are more likely to develop complications such as infections, gastrointestinal haemorrhage, or hyperglycaemia. This may occur despite stratified randomisation, particularly when the numbers are few in the individual stratum. Argu-

ably, similar factors in our placebo group may explain our findings. This may be true, but it emphasises the few and hence not very reliable data on whether dexamethasone is too unsafe to be used.

We conclude that dexamethasone in the regimen used in our trial is not likely to produce an unacceptably high rate of adverse effects in patients with primary supratentorial intracerebral haemorrhage. Whether or not dexamethasone or other corticosteroids are beneficial in this setting needs further study. The study by Pongvarin *et al.*⁴ points to a higher proportion of patients making complete recovery by the 21st day in the treatment group (odds ratio 0.7, 95% CI, 0.2–2.4), this needs to be either confirmed or refuted.

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Clinical characteristics, complications, and outcome of patients

	Dexamethasone (n=12)	Placebo (n=14)
Age (mean (SD))	58.3 (11.7)	59.8 (7.4)
Haemorrhage to treatment (h, mean (SD))	30.3 (31.8)	27.2 (29.7)
Glasgow coma scale scores:		
3–7	5	3
8–11	2	6
12–14	5	5
Volume of haematoma (ml, mean (SD))	34 (36.4)	35.7 (35.3)
Location of haematoma:		
Basal ganglia	7	8
Thalamus	3	3
Lobar	2*	3†
Intraventricular leakage of blood	8	8
Mean (SD) arterial pressure (mm Hg)	123.9 (13.9)	133.8 (20.2)
Complications:		
Infections‡	3	7
Gastrointestinal bleeding§	0	2
Diabetogenic effect¶	1	1
Reasons for stopping allocated treatment:		
Gastrointestinal bleed	0	2
Abdominal distension	0	1
Jaundice	0	1
Wrong diagnosis	1	1
Outcome at discharge:		
Death		
Due to herniation	5	1
Due to infection	0	1
Vegetative	0	1
Dependent	5	9
Independent	2	2

* One patient had haemorrhagic infarct. †One patient had aneurysmal bleed. ‡Infection which was not present or suspected at the time of admission to the study. §Includes overt gastrointestinal bleed (haematemesis, bloodstained gastric aspirate or melaena; and clinically important gastrointestinal bleed (overt gastrointestinal bleed with either, a fall in systolic blood pressure >20 mm Hg within 2 hours of bleeding; fall in haemoglobin >2 g/dl; blood pressure reduction >10 mm Hg; and increase in heart rate >20 beats/minute on orthostatic change; or need for blood transfusion). ¶Fasting sugar >160 mg/dl, requiring regular insulin in a patient who was not previously considered to have diabetes, and who was not receiving glucose.

Postpartum cerebral venous thrombosis, congenital protein C deficiency, and activated protein C resistance due to heterozygous factor V Leiden mutation

Activated protein C resistance (APC-R) due to factor V Leiden mutation is the most common thrombophilia associated with cerebral venous thrombosis. It is present in 10% to 20% of patients but usually in association with other constitutional or acquired prothrombotic conditions.¹ We present a case of postpartum cerebral venous thrombosis in a patient with protein C deficiency and APC-R due to heterozygous factor V Leiden mutation. In addition to puerperium, the role of intravenous steroids is questioned in this case.

A 33 year old woman was admitted because of severe subacute headaches, nausea, and drowsiness. She was not taking oral contraceptives. Her medical history disclosed recent delivery of a second child 3 weeks before and an asthma attack 5 days before entry, treated with intravenous methylprednisolone (120 mg daily). Family history disclosed that the patient's mother had had postpartum lower limb deep vein thrombosis. On admission, clinical examination disclosed papilloedema. There was no fever and no ear, nose, or throat infection. Brain CT showed a right temporal hypodensity, a delta sign, and small ventricles. Brain MRI (with MRA) demonstrated recent superior sagittal sinus, and right and left lateral sinus thrombosis. High dose intravenous heparin was immediately initiated. Heparin treatment was switched to warfarin after 10 days. At 3 months, neurological examination was normal. Follow up MRA showed complete recanalisation of the superior sagittal sinus and the right lateral sinus, and partial recanalisation of the left hypoplastic lateral sinus. Oral anticoagulation was maintained at International Normalized Ratio (INR)

between 2 and 3). One year later, the patient is still symptom free under this treatment. The proband investigations were performed twice: during acute phase thrombosis and seven months later when the patient had temporarily discontinued oral anticoagulation therapy. Four other family members (the father, the mother, and two sisters) were available for examination (figure and table). The proband (II.2) exhibited qualitative protein C deficiency and APC-R due to heterozygous factor V Leiden mutation. Protein S activity and antithrombin III concentrations were normal. Search for antinuclear antibodies, anticardiolipin antibodies, and lupus anticoagulant, dysfibrinogenemia, or plasminogen deficiency was negative. Plasma homocysteine concentration was normal. The father (I.1) had APC-R due to heterozygous factor V Leiden mutation. The mother (I.2) had a qualitative protein C deficiency. The first sister (I.1) had no APC-R nor protein C deficiency. The second sister (II.3), who had one pregnancy without any thrombotic event, had both protein C deficiency and APC-R due to heterozygous factor V Leiden mutation.

Our patient presented an extensive postpartum cerebral venous thrombosis with a double inherited coagulation defect: protein C deficiency and APC-R due to heterozygous factor V Leiden mutation. To our knowledge, the coexistence of these two thrombophilias has not been previously described in a patient with cerebral venous thrombosis. Genetic study showed that APC-R due to factor V Leiden mutation was transmitted by the

patient's father and that protein C deficiency was transmitted by the patient's mother.

The protein C anticoagulant pathway is triggered when thrombin binds to the endothelial cell receptor thrombomodulin. This interaction converts thrombin into a potent protein C activator while blocking the fibrinogen clotting and platelet activating activity of thrombin. Activated protein C then serves as an anticoagulant by inactivating factors Va and VIIIa.² In our patient, acquired causes of protein C deficiency could be excluded. We diagnosed a congenital protein C deficiency with an autosomal dominant mode of inheritance. A type I deficiency could be postulated according to the reduction of both antigen concentration and activity of protein C, reduction of activity but normal antigen concentration being present in type II. Only a few cases of cerebral venous thrombosis with congenital protein C deficiency have been reported so far.^{3,4} Inherited protein C deficiency seemed to be the sole risk factor for thrombosis in some cases¹ whereas other prothrombotic conditions such as the postpartum period were present in other cases.³ Additional risk factors for thrombosis might be necessary for thrombotic manifestations to appear in patients with protein C deficiency as the heterozygous state is usually asymptomatic with an estimated prevalence of 1 in 200 to 300.⁴

In 1993, Dahlbäck *et al* described a new pathological condition termed APC-R, characterised by a poor anticoagulant response to activated protein C. This coagulation disorder is often associated with a single point mutation in one or both alleles of the factor V gene (adenine substituted for guanine at

nucleotide 1691, the so called Leiden mutation) at a site of cleavage by activated protein C which delays inactivation of coagulant factor Va. The prevalence of the factor V Leiden mutation varies by geography and ethnicity, ranging from 2% to 15% in healthy white people. Factor V Leiden mutation is inherited as an autosomal dominant trait and most heterozygous people do not have clinical thrombotic complications. The odds ratio for venous thrombosis has been calculated to be 3.8-fold for heterozygous patients.⁵ An important similarity of patients with APC-R and cerebral venous thrombosis is the frequency of other associated risk factors for thrombosis. Sixteen of 18 reported cases showed another genetic or acquired thrombosis risk factor: oral contraceptives in eight, pregnancy/puerperium in four, nephrotic syndrome in one, intravenous steroids in one, immobilisation in one, primary antiphospholipid antibody syndrome in one, and antithrombin III deficiency in one.¹ These data suggest that the association of APC-R with another prothrombotic state is crucial in the occurrence of cerebral venous thrombosis. In our patient, APC-R was associated with congenital protein C deficiency and two other acquired prothrombotic risk factors, postpartum and intravenous steroid therapy. The prothrombotic risk of intravenous steroids is questioned in our patient as she had not experienced any thrombotic event during her first pregnancy and postpartum period. It is noticeable that the patient's sister (II.3) with APC-R and protein C deficiency had had one child without venous thrombosis. The prothrombotic risk of intravenous steroids should be considered in patients with

Pedigree of the family. The three generations are indicated by roman numbers. Arabic numbers indicate the family members who have been investigated. Square=male; circle=female; no deficiency open; protein C deficiency hatched; factor V Leiden black; *positive thromboembolism history. The proband is indicated by an arrow.

Biological data of the proband (II.2) and her family

Patient	Sex	Age	VT	FVL	APC-NR	PC (%)		
						Coag	Chrom	Ag
I.1	M	69	No	Yes	0.55	84	ND	ND
I.2	F	66	Yes	No	0.83	50	57	56
II.1	F	37	No	No	0.82	101	ND	ND
II.2*	F	33	Yes	Yes	0.53	61	68	78
II.2**		35			0.60	32	39	38
II.3	F	31	No	Yes	0.51	35	45	52
Normal values					>0.82	>70	>70	>70

VT=venous thrombosis; FVL=Leiden factor V; APC-NR=activated protein C resistance normalized ratio; PC=protein C; Coag=coagulant activity; Chrom=chromogenic activity; Ag=antigen; ND=not done; *II.2 proband coagulation screening during acute phase thrombosis; ** seven months later, without oral anticoagulant treatment.