Guillain-Barré syndrome after exogenous gangliosides in Italy

Gianluca Landi, Roberto D'Alessandro, Bruno Currò Dossi, Stefano Ricci, Isabella Laura Simone, Alfonso Ciccone

Clinica Neurologica, Ospedale Policlinico, 20122 Milan, Italy
Gianluca Landi
Alfonso Ciccone

Servizio di Neurologia, Policlinico S Orsola, Bologna, Italy
Roberto D'Alessandro

Divisione Neurologia, Ospedale degli Infermi, Rimini, Italy
Bruno Currò Dossi

Clinica Neurologica, Ospedale Policlinico, Perugia, Italy
Stefano Ricci

Istituto di Clinica delle Malattie Nervose e Mentali, Università di Bari, Italy
Isabella Laura Simone

Correspondence to:
Dr Landi.

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Exogenous gangliosides are marketed in several countries and used to treat many neurological diseases. Although no well designed clinical trial has convincingly shown their efficacy in diseases of the peripheral or central nervous system, they are widely prescribed, at least in Italy. An estimated 4.1% of the population in Rome were prescribed gangliosides in 1989,¹ and in 1991 around 4.2% of the 687 401 people from five local health districts in the Emilia Romagna region received the drugs (N Montanaro, *et al*, personal communication).

The safety of exogenous gangliosides has been questioned. They were withdrawn in Germany because six patients developed the Guillain-Barré syndrome after taking them. Latov *et al* reported a similar case with high titres of antibodies to monosialoganglioside²; they suggested that gangliosides may induce an immune response when made into a complex with serum or tissue proteins. Figueras *et al* described 17 cases of motor polyneuropathy after ganglioside administration; at least eight of the patients had received the drug for unrelated conditions.³ We report 24 further cases of the Guillain-Barré syndrome after ganglioside treatment.

Patients and results

To gather information on the development of the Guillain-Barré syndrome after administration of gangliosides a form was sent to all centres that were believed through direct contact or information from other centres to have admitted such patients. We obtained data on 24 patients from 18 Italian hospitals who between January 1989 and July 1993 developed the syndrome within three weeks of starting ganglioside treatment. The syndrome was diagnosed in all cases by a neurologist according to the National

Institute of Neurological Disorders and Stroke criteria. Fifteen patients had received a fixed mixture of gangliosides while the others had been treated with purified monosialoganglioside. The characteristics of the patients are summarised in the table. The indications for ganglioside treatment as well as the interval between its start and the onset of the syndrome make it unlikely that they were given for unrecognised presentations of the Guillain-Barré syndrome. Examination of cerebrospinal fluid disclosed albumino cytological dissociation in 22 cases; the two other patients did not show pleocytosis. Overall 21 of the 22 patients who underwent neurophysiological evaluation had findings consistent with polyneuropathy.

Comment

Our 24 patients were found through direct contact with a few hospitals and probably underestimate the actual number of cases. Yet given an incidence of 1.7 per 100 000 people per year (or 0.1 per 100 000 per 3 weeks) of the Guillain-Barré syndrome and a yearly exposure to gangliosides of 4.5% among less than 60 million people living in Italy, these 24 cases exceed those expected by chance in the whole of the country among subjects taking gangliosides. That our patients may represent a peculiar subgroup of the Guillain-Barré syndrome is suggested by their low prevalence of antecedent infections (12.5%, 95% confidence interval 2.7% to 32.4%), which contrasts with the prevalence of 50-70% reported in most epidemiological surveys. Moreover, 66.7% (38.4% to 88.2%) of the 15 subjects for whom this information was available had raised titres of antibodies to monosialoganglioside. Although their role in the Guillain-Barré syndrome is debated, these antibodies had raised titres in only 30% of patients with the syndrome who had not taken exogenous gangliosides.⁴

As the therapeutic efficacy of gangliosides is unproved, we think that the ratio of risk to benefit may be unfavourable for these drugs. An epidemiological study failed to detect an association between gangliosides and the Guillain-Barré syndrome,⁵ but because of the small sample size it could not reliably exclude even a 200-fold increase of risk among patients treated with gangliosides. Until larger epidemiological surveys allow better definition of this risk, health authorities in countries where these drugs are marketed should

Clinical features of 24 patients with Guillain-Barré syndrome after ganglioside treatment

Case No	Sex	Age (years)	Time from start of gangliosides to onset of syndrome (days)	Indication for gangliosides	Prodromal respiratory or gastrointestinal infection	Serum monosialoganglioside antibody titre*	Residual neurological deficit (months of follow up)†
1	F	64	11	Relapsing ankle pain	None	Very raised	Moderate (6)
2	M	44	10	Lumbago	None	Very raised	Moderate (7)
3	M	36	14	Arm pain	None	Mildly raised	Moderate (12)
4	M	45	10	Head trauma	None	Normal	Moderate (6)
5	M	61	13	Trigeminal pain	None	Very raised	Severe (30)
6	F	40	11	Multiple sclerosis	Flu-like illness	NA	Moderate (36)
7	M	61	10	Bell's palsy	None	Normal	None (12)
8	F	70	6	Previous cerebellar haemorrhage	None	NA	Dead (0.5)
9	M	58	11	Lumbago	None	Very raised	Moderate (24)
10	M	60	4	Previous lumbago	None	Very raised	Severe (5)
11	F	58	8	Bell's palsy	None	NA	Severe (6)
12	M	40	8	Cerebral haemorrhage	Bronchopneumonia	NA	Severe (6)
13	F	69	18	Stroke	None	Mildly raised	Moderate (2)
14	M	31	6	Post-traumatic headache	None	Normal	Moderate (3)
15	M	49	15	Neurosurgery for cerebral metastasis	None	NA	Severe (4)
16	F	42	10	Lumbago with sciatic pain	None	NA	None (2)
17	F	39	7	Arm pain	None	NA	Moderate (3)
18	M	31	15	Lumbago with sciatic pain	None	NA	None (8)
19	M	58	5	Visual loss	Upper respiratory tract	Normal	None (10)
20	M	80	14	Minor stroke	None	Very raised	Moderate (12)
21	M	83	13	Transient right hand paraesthesias	None	Normal	Dead (1)
22	F	62	6	Lumbago with sciatic pain	None	NA	Severe (2)
23	F	83	16	Parkinsonism	None	Very raised	Moderate (4)
24	F	63	4	Chronic hearing loss	None	Very raised	Severe (1)

NA=not available.

*Enzyme linked immunosorbent assay (ELISA).

†Severe=serious residual motor signs, unable to walk; moderate=able to walk; none=no residual motor signs.

consider that a large number of patients may remain exposed to a rare but severe adverse effect.

Another case was reported to us after submission of the manuscript. In July 1993 a 63 year old man developed the Guillain-Barré syndrome after treatment for 10 days with purified monosialoganglioside for a stroke. This is the third case to be reported to us in 1993.

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Are clinicians interested in up to date reviews of effective care?

Sara Paterson-Brown, Jeremy C Wyatt,
Nicholas M Fisk

Institute of Obstetrics and
Gynaecology, Royal
Postgraduate Medical
School, Queen Charlotte's
and Chelsea Hospital,
London W6 0XG

Sara Paterson-Brown, senior
registrar
Nicholas M Fisk, professor

Imperial Cancer Research
Fund, London WC2A 3PX
Jeremy C Wyatt, medical
informatics manager

Correspondence to:
Miss Paterson-Brown.

One of the first initiatives of the new NHS research and development strategy is the funding of the Cochrane Centre to prepare and disseminate systematic reviews of evidence based practice. This assumes that doctors will use them. Obstetrics was the first specialty to have access to such reviews with the Oxford Database of Perinatal Trials. This has been available on computer disk for four years, is updated every six months, and contains meta-analysis of randomised controlled trials in perinatal medicine. This study ascertains current awareness and use of this database.

Methods and results

We conducted a telephone survey of all 24 teaching hospitals and 74 of the 173 district hospitals in England. Of the district general hospitals in each of the 14 regional health authorities, at least a third (a minimum of four) were sampled. One of us (SP-B) interviewed either the administrative contact of the Royal College of Obstetricians and Gynaecologists (in 83 of the cases) or a suitable colleague (always a consultant; in 15 cases) with a standardised questionnaire between February and May 1993. Interviewees were aware that their responses would not be attributed to individual hospitals or doctors. All the nominated consultants were successfully contacted, and when this required multiple attempts the interviewee was not forewarned of our purpose.

Of the 24 teaching hospital consultants, 23 had heard of the Oxford database, as had 61 of the 74 from district general hospitals, but only 13 (54%) and 15 (20%) respectively were able to define it. It was unavailable in nine teaching hospitals—four considered it too expensive and two thought that they did not need it—

and in 62 district general hospitals—reasons given included the hospital not being computerised (in seven cases) and not needing it (10). In the units with the database, however, it was used by all grades of doctor between once a week and once a month.

Comment

This survey shows that systematic overviews of evidence based practice are not currently well disseminated, with 72% of the obstetric units surveyed not having access to a copy of the database of obstetric trials. Despite publicity and support for such overviews in obstetrics¹⁻³ lack of awareness was shown to be an important factor, as 14% of obstetric consultants had never heard of the database and only 29% could define it. We also questioned interviewees on their awareness and possession of the now outdated textbook version (*Effective Care in Pregnancy and Childbirth*) advocated in the maternity services report⁴ and will report the findings elsewhere.

Among the reasons given for not having the database, seven obstetric units in district general hospitals did not have access to a computer, which is surprising. Another reason given was one of expense: in 1989 the database cost about £600, in 1991 about £250, but now, produced by The Cochrane Collaboration, it costs £56.40 a year for a personal copy or £98.70 for an institution. The justification given for some units not having the database revealed entrenched attitudes: "Obstetrics is an art not a science"; "We are a teaching hospital so we don't need to know what everyone else does"; and "We have been able to avoid writing protocols to date."

Obstetricians have been singled out for having unscientific and inconsistent practices.⁴ Clinical protocols are becoming more popular, but without access to the database incorrect management policies will remain widespread. An example of this is a recent article in the *BMJ* which contains advice on the management of post-term pregnancy that is in contradiction to the database.⁵ Up to date reviews of effective care may have medicolegal relevance in the future.

Despite its obvious benefits, the database is neither widely disseminated nor widely used. These problems should be noted by other branches of medicine now trying to disseminate systematic reviews of effective care.

Availability and use of Oxford Database of Perinatal Trials in 98 obstetric units in England. Values are numbers (percentages) of units

	Teaching hospitals (n=24)	District general hospitals (n=74)
Database unavailable	9 (38)	62 (84)
Database available and used for:	15 (62)	12 (16)
Planning research	8	1
Finding references	11	6
Education	13	7
Designing protocols	10	8
Specific patient problems	2	6
Unknown	1	2

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