Neurosciences Grand Rounds
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Pain and Sensory Symptoms in Guillain-Barré Syndrome

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Outline

- Introduction
- Case Presentations
- Defining the Clinical Presentation of GBS
- Sensory Symptoms in GBS
- Pain in GBS
  - Pharmacologic management
- Conclusions

Introduction

- Two cases of Guillain-Barré Syndrome (GBS) seen while on the Neurology service last year were the inspiration for this talk
- I will present their cases and discuss how they led me to explore the problem of pain in GBS.
- Hopefully, I will answer the following-
  - How common is pain in GBS?
  - What types of pain do patients experience?
  - What treatments are effective?

Case One

- 26F presented to local hospital c/o “worst headache of her life” and numbness/tingling of extremities
  - One week prior history of migrainous headache
  - Three week history of malaise, myalgias, fevers/chills, night sweats
  - Unsteady while walking
- Physical exam
  - Meningeal signs
  - Tender hepatomegaly - ? (not consistently reported)
- Initial diagnosis – probable viral meningitis

Case One

- Investigations
  - CSF: WBC 1, RBC 2, prot 0.74 g/L, gluc 3.1 g/L
  - Abdominal U/S: mild hepatomegaly
  - Serology: EBVCA IgM positive, EBNA negative
- Course in local hospital
  - PAD #3: unable to rise from bed or walk to washroom unaided
  - Absent lower extremity DTRs
- Transferred to UAH for treatment of GBS

Case One

- Admission physical examination
  - Bilateral facial weakness
  - UE power 4-/5 bilaterally
  - LE power 4/5 bilaterally
  - Absent DTRs except left biceps
  - Diminished pinprick and vibration sensation in all extremities
- Started on admission on IVIg at 2 gm/kg
- Arrived to UAH near the nadir of her weakness
  - Did not require ventilatory support

Case One

- Pain issues throughout her ten-day stay
  - Headache and neck stiffness
    - Exacerbated by transfusion reaction on day #3 of IVIg
      - Treated with IV steroids
    - Some response to triptans and NSAIDs
  - Aching limb pains
    - Muscle soreness
    - At times limiting attendance at physiotherapy
  - Started on gabapentin near time of discharge
- Returned to local hospital for further convalescence

Case Two

- 60M presents with distal limb numbness
  - Onset 2-3 weeks prior, while on vacation in US
  - One week later, perioral/tongue numbness
  - Gradually ascending numbness up to knees/wrists
  - No weakness initially - ?
  - Headache and back stiffness
  - Seen in US – investigations for cervical myelopathy and polyneuropathy
- Returns to Edmonton, sees an outpatient neurologist
  - referred to UAH, for polyneuropathy, ?GBS

Case Two

- While in hospital, symptoms progressed
  - No sensation in feet and hands (except 5th digit)
  - Dysphonia and dysphagia
  - Gait slow and clumsy
  - Developed objective weakness
    - Proximal and distal
    - Initially able to ambulate with a 4WW
- Deep tendon reflexes intact on admission
  - Lost ankle jerks on PAD #2

Case Two

- CSF (PAD #3):
  - 2 WBC, 1 RBC, Gluc 4.0 mmol/L, prot 1.26 g/L
- EMG/NCS (PAD #4):
  - Severely prolonged motor latencies
  - Slowed conduction velocity
  - No evidence of denervation
  - No sensory responses elicited
  - Findings c/w acute inflammatory demyelinating polyneuropathy

Case Two

- Treated with IVIg, minimal improvement noted
- Developed painful paresthesias in his extremities
  - Started on gabapentin and acetaminophen
- Ambulation impaired by weakness and considerable sensory deficit
- One month post-admission, transferred to Glenrose Rehabilitation Hospital
  - Some improvement of strength on admission, but still clumsy and uncoordinated – “element of sensory ataxia” noted

Case Discussion

- Two case presentations of GBS
- Common themes:
  - Sensory symptoms on presentation before development of weakness/areflexia
  - Pain was a significant issue during the acute phase of illness (long-term?)
  - Sensory symptoms persistent as motor deficits stabilized or improved

Case Discussion

- Were these typical cases?
  - Does “typical” GBS present with prominent sensory findings, and/or pain?
- What is a typical case of GBS?
- What are “atypical” cases?

Defining GBS

- “The clinical aphorism that the Guillain-Barré syndrome is easy to diagnose but impossible to define is as true today as it has been in the past”
  - Munsat and Barnes, 1965

Defining GBS

- Weakness evolving over weeks in the hips and legs, then arms, frequently involving the face and respiratory muscles, and less often eye movements
- Paresthesias in the toes and fingertips that advance proximally
- Eventual loss of deep tendon reflexes
- Spontaneous gradual recovery over weeks to months
- Elevated CSF protein concentration with few cells
- (electrophysiologic abnormalities)

Ropper AH et al, 1991

Sur un syndrome de radiculo-névrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire. Remarques sur les caractères cliniques et graphiques des réflexes tendineux,

par MM. Georges Guillain, J.-A. Barré et A. Strohl.

Nous attirons l'attention, dans la présente note, sur un syndrome clinique que nous avons observé chez deux malades, syndrome caractérisé par des troubles moteurs, l'abolition des réflexes tendineux avec conservation des réflexes cutanés, des paresthésies avec troubles légers de la sensibilité objective, des douleurs à la pression des masses musculaires, des modifications peu accentuées des réactions électriques des nerfs et des muscles, de l'hyperalbuminose très notable du liquide céphalo-rachidien avec absence de réaction cytologique (dissociation albumino-cytologique). Ce syndrome nous a paru dépendre d'une atteinte concomitante des racines rachidiennes, des nerfs et des muscles, vraisemblablement de nature infectieuse ou toxique. Il doit être différencié des radiculites simples, des polynévrites pures et des polymyosites. Des recherches expérimentales par la méthode graphique sur la vitesse des réflexes et leur temps perdu, sur les modalités, la contractilité musculaire, montrent la réalité de la participation, dans ce syndrome, de tout l'appareil moteur neuro-musculaire périphérique. Nous insistons particulièrement aussi sur l'hyperalbuminose du liquide céphalo-rachidien sans réaction cytologique, fait qui, à notre connaissance, n'a pas été mentionné dans des cas semblables.

Defining GBS

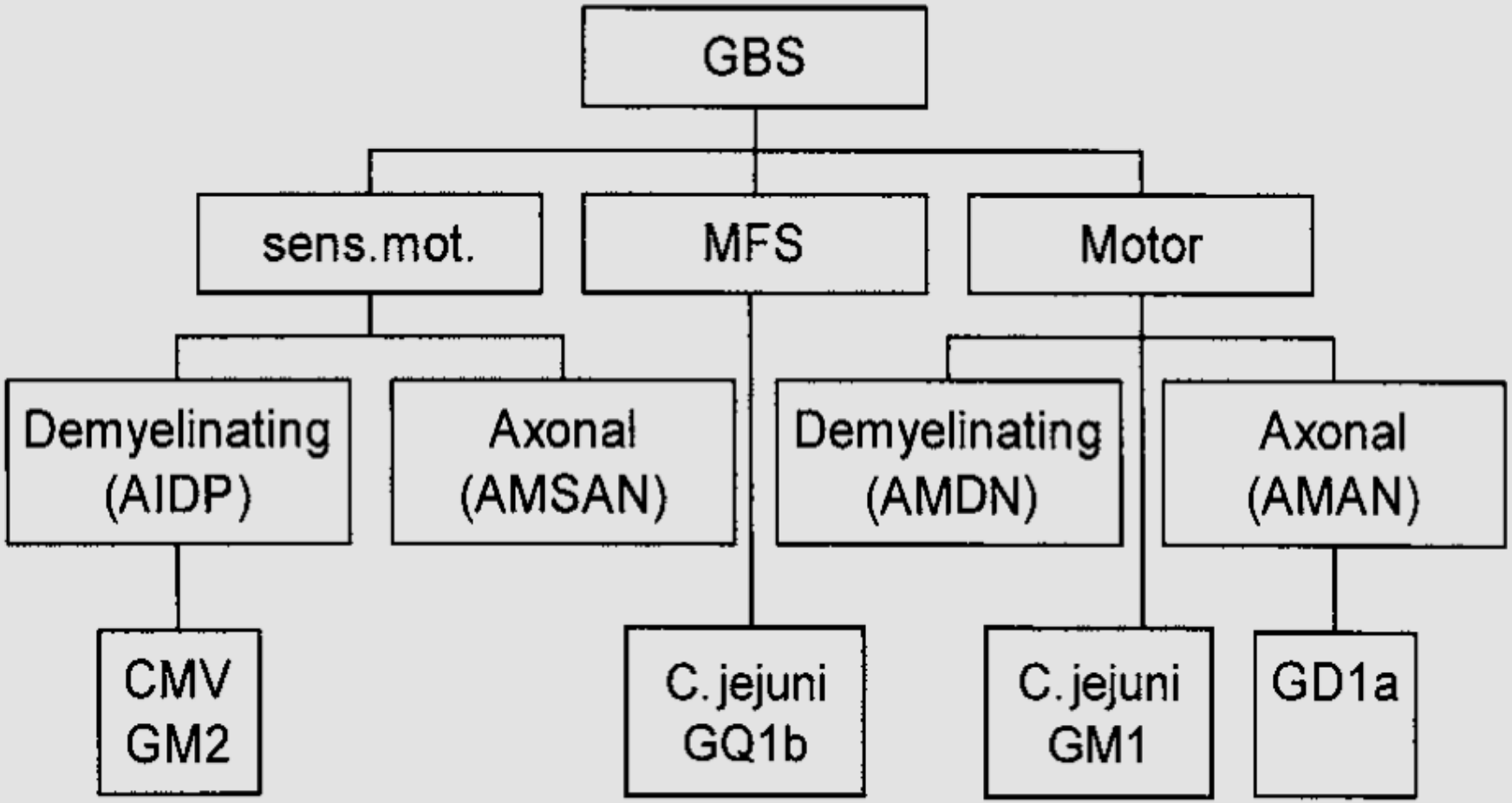
- Syndrome caractérisé par...
  - Troubles moteurs
  - Paresthésies avec troubles légers de la sensibilité objective
  - L'abolition des réflexes tendineux
  - Douleurs à la pression des masses musculaires
  - L'hyperalbuminose très notable de liquide céphalo-rachidien avec absence de réaction cytologique (dissociation albumino-cytologique)

Guillain,G., Barre,J.A., and Strohl,A. (1916). Bul Soc Méd Hôp Paris; 40:1462-70

Criteria for Defining GBS

- Diagnostic Criteria (WHO 1993 criteria)
  - Symmetrical weakness
  - Disappearance or decrease of myotatic reflexes
  - Nadir of symptoms within 4 weeks of onset
  - Other diagnoses unlikely
- These criteria do not address subgroups or “variant” or “atypical” presentations of GBS

GBS Classification



Van der Meché et al. Eur Neurol (2001) vol. 45 (3) pp. 133-9

Motor-Sensory GBS

- The "classical" syndrome as described by Guillain
  - About 75% of cases in the Western world
- Includes (note: CSF and EMG/NCS findings supportive but not necessary)
  - Subacute course
  - Symmetric weakness
  - Loss of deep tendon reflexes
  - Other causes of flaccid paralysis excluded
  - Sensory deficit
    - "large variability in severity of sensory deficit"
    - Paresthesias, sensory ataxia... pain?

Van der Meché et al. Eur Neurol (2001) vol. 45 (3) pp. 133-9

Neurologic Findings in GBS

- Described in numerous case series, e.g. Massachussets General Hospital
- Initial symptoms
  - Pain, 26%
  - Paresthesias, 38%
- Cumulative symptoms after progression
  - Pain, 71%
  - Numbness/Paresthesias, 72%

Table 7–3 NEUROLOGIC FINDINGS IN RETROSPECTIVE MGH SERIES (N = 169)

Initial Symptoms	
Weakness + paresthesias	26%
Weakness + pain	14%
Weakness alone	12%
Weakness + pain + paresthesias	12%
Pattern of weakness	
Legs>Arms	54%
Arms>Legs	14%
Approximately equal	32%
Cumulative Symptoms after Progression (Includes Variants)	
Weakness	98%
Numbness/Paresthesias	72%
Pain	71%
Cranial nerve symptoms (except face)	40%
Ataxia	22%
Sphincter symptoms	18%

Tendon Reflexes on Admission (168 Patients)

Reflex*	2+	1+	0	Asymmetric
Biceps	20%	23%	57%	4%
Brachioradialis	13%	19%	68%	2%
Triceps	16%	22%	62%	6%
Quadriceps	8%	13%	59%	5%
Gastrocsoleus	4%	8%	88%	0%

2+ = normal; 1+ = reduced; 0 = absent.

Ropper AH et al, 1991

Sensory symptoms in GBS

Table 7–1 NEUROLOGIC FINDINGS AT INITIAL EXAMINATION IN LARGE SERIES*

Series, Year	No. of Patients	Cranial Nerve Abnormalities					Distribution of Weakness				Sensory Loss (%)	Areflexia (All Limbs) (%)	Pain (%)
		III-VI (%)	V (%)	VII (%)	IX-X (%)	XII (%)	L	A	L&A	N			
Wiederholt et al.,[1278] 1964	97	5	0	29	1	1	8	2	85	5	38	52	14
McFarland and Heller,[777] 1966	100	6	15	55	48	10	24	1	74	1	70	NA	15
Andersson and Siden,[31] 1982	60	2	8	25	6	0	2	10	83	5	50	85	3
Winer et al.,[1291] 1988	100	13	31	53	46	13	0	0	100	0	59	83	50

*Percent of patients.

Table 7–2 CUMULATIVE NEUROLOGIC FINDINGS IN LARGE SERIES

Series, Year	No. of Patients	Cranial Nerve Abnormalities					Distribution of Weakness (%)				Sensory Loss (%)	Areflexia/ Hyporeflexia (%)
		III-VI (%)	V (%)	VII (%)	IX-X (%)	XII (%)	L	A	L&A	N		
Haymaker and Kernohan,[501] 1949	50	18	28.0	50	94	20	44	14	42	0	38	NA
Marshall,[751] 1963	35	28	23.0	60	54	54	3	0	97	0	47	100
Ravn,[973] 1967	127	18	3.0	36	31	6	6	2	86	6	NA	NA
Loffel et al,[714] 1977	123	7	0.8	29	23	5	14	2	80	4	83	100
Soffer et al,[1122] 1978	89	7	0	24	13	1	38	0	60	2	37	24
Samantray et al.,[1053] 1977	302	2	7.0	46	13	0	94	1	4	1	0	NA

NA = Not available.

Ropper AH et al, 1991

Sensory Symptoms in GBS

- Sensory symptoms were nearly as common as motor findings in these case series
- Pain was a common symptom in these case series
  - In the acute phase of illness
  - Persisting beyond the nadir of motor weakness
- *Pain is a key feature of Guillain-Barré Syndrome*
- More recent studies focusing on pain/disability in GBS have found higher incidences of pain
  - Ranging from 47-89% of patients (see table)

Reference	Pain (pts/n, %)	Comment
Andersson and Sidén. Acta Neurol Scand (1982) vol. 66 (3) pp. 316-27	2/60, 3%	Pain as presenting symptom - 10 patients (17%) developed "neuralgic pains" later in their course
Ropper and Shahani. Arch Neurol (1984) vol. 41 (5) pp. 511-4	16/29, 55%	Pain early in illness
Winer et al. J Neurol Neurosurg Psychiatr (1988) vol. 51 (5) pp. 605-12	50/100, 50%	time-point unclear (at study entry?), total duration of follow-up was 52 weeks
Moulin et al. Neurology (1997) vol. 48 (2) pp. 328-31	47/55, 85%	pain at time of admission, 89% of patients had pain during the course of their illness
Bernsen et al. J Neurol (2001) vol. 248 (6) pp. 483-6	59/122, 48%	Muscle aches and cramps; 3-6 yrs follow-up
Forsberg et al. J Neurol Sci (2004) vol. 227 (1) pp. 131-8	30/42, 71%	Pain at two weeks from onset of symptoms
Ruts et al. J Neurol (2007) vol. 254 (10) pp. 1318-22	123/223, 55%	Data extracted from: van Koningsveld et al. Lancet (2004) vol. 363 (9404) pp. 192-6)
Ruts et al. J Peripher Nerv Syst (2008) vol. 13 (4) pp. 305-6	39/83, 47%	Pure motor syndrome in 60 of these patients; of whom 26 had pain (43%)
Rekand et al. J Neurol (2009) vol. 256 (3) pp. 349-54	34/50, 68%	Retrospective study, median 10 yrs from dx
Ruts et al. Neurology (2010) vol. 75 (16) pp. 1439-47	100/152, 66%	pain at time of diagnosis

Pain in GBS – Physician accounts

- “The paralysis, weakness, and ataxia were frightening enough, but perhaps the most devastating thing was the pain, which was periodic and excruciating and always worst at night.”
  - Rice, 1977
- “...the nights were endless. I couldn't sleep from the unbearable pain. It felt as if my skin were being pulled off my body. I thought of death frequently...”
  - Shearn MA and Shearn L, 1986

Pain in GBS – Physician accounts

- "No matter how detached one tries to be, a vital capacity of 600-700 ml and continued excruciating, burning pain in the back and in all other pressure areas tends to cause one to form likes and dislikes quickly... the relentless burning pain in all pressure areas, and a peculiar sensation of lying on wrinkled sheets or on a lumpy mattress, paralyzed, tracheostomized, and with an indwelling Foley catheter, made life, to put it mildly, somewhat narrow."
  - Henschel, 1977

Pain in GBS

- There are multiple types of pain in GBS
  - Differing in quality, location, and time of onset
  - Many studies lump all types of pain together
  - Evidence regarding treatment of pain is confined to the acute phase
- Discrete pain syndromes in GBS patients
  - Back and radicular-type leg pain in the acute phase
  - Dysesthetic extremity pain (burning, shock-like)
  - In acute and later phases, deep aching muscle pain

Pain in GBS

- Ropper and Shahani prospectively studied pain in a series of 29 GBS patients
  - seen within 15 days of onset of weakness
  - 16 (55%) of patients had pain
  - 12 of these patients had deep aching muscle pains – similar to very strenuous exercise
  - 6 patients developed muscular pain up to 3 weeks after the onset of illness
  - 6 patients reported severe pain, 8 patients moderate pain, and 2 moderate pain
  - In all patients, pain was worst at night

Ropper and Shahani. Arch Neurol (1984) vol. 41 (5) pp. 511-4

Pain in GBS

- Moulin et al (1997) prospectively followed a series of 55 GBS patients for a total of 24 weeks
  - 47 (89%) developed pain during the study

Table 2 *Pain syndromes observed in Guillain-Barré syndrome (N = 55)*

Back and leg pain	34 (61.8%)
Dysesthetic extremity pain	27 (49.1%)
Myalgic-rheumatic extremity pain	19 (34.5%)
Visceral pain	11 (20%)
Pressure palsy (ulnar nerve)	1 (2%)
Headache caused by dysautonomia	1 (2%)

Moulin et al. Neurology (1997) vol. 48 (2) pp. 328-31

Pain in GBS

- Early studies of pain in GBS tend to recruit small patient numbers, have short follow-up, and many are retrospective case series
- Recent prospective study of pain in GBS
  - Ruts et al. Pain in Guillain-Barre syndrome: a long-term follow-up study. Neurology (2010) vol. 75 (16) pp. 1439-47

Ruts et al, 2010

- The largest prospective study of pain in GBS to date
  - Gathered cases from 55 centres in the Netherlands
  - Enrolled 170 subjects, 14 excluded
  - 138 GBS cases, 18 MFS cases

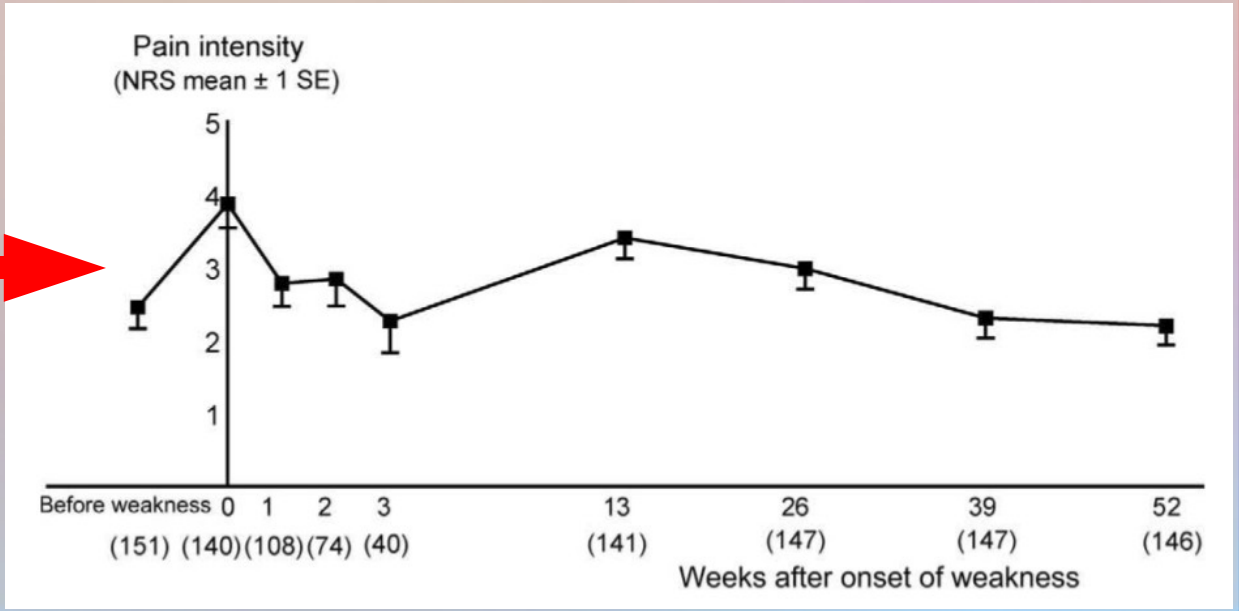
Acute phase,[b] n (%)	
Signs and symptoms	
Cranial nerve involvement (n = 153)	81 (53)
Sensory symptoms (n = 152)	132 (87)
Sensory disturbances (n = 150)	98 (65)
Severity at nadir	
Severely affected (unable to walk unaided)	126 (81)
Respiratory support	28 (18)

Ruts et al. Neurology (2010) vol. 75 (16) pp. 1439-47

Ruts et al, 2010

- Pain assessed at the acute phase (at time of diagnosis) as well as
  - 2 weeks before onset of weakness (retrospective)
  - At 13 wks, 26 wks, 39 wks, 52 wks
- 66% of patients had pain in the acute phase of illness

Taking the mean of a categorical variable (NRS) underplays the presence of severe pain in some patients



Ruts et al. Neurology (2010) vol. 75 (16) pp. 1439-47

Ruts et al, 2010

- 50% of all patients suffered severe pain (NRS 8-10) in the acute phase of illness
- Pain was more prevalent in patients with sensory disturbance (t = 0: 62% vs 43%; t = 6 mos: 56% vs 34%; p<0.05)

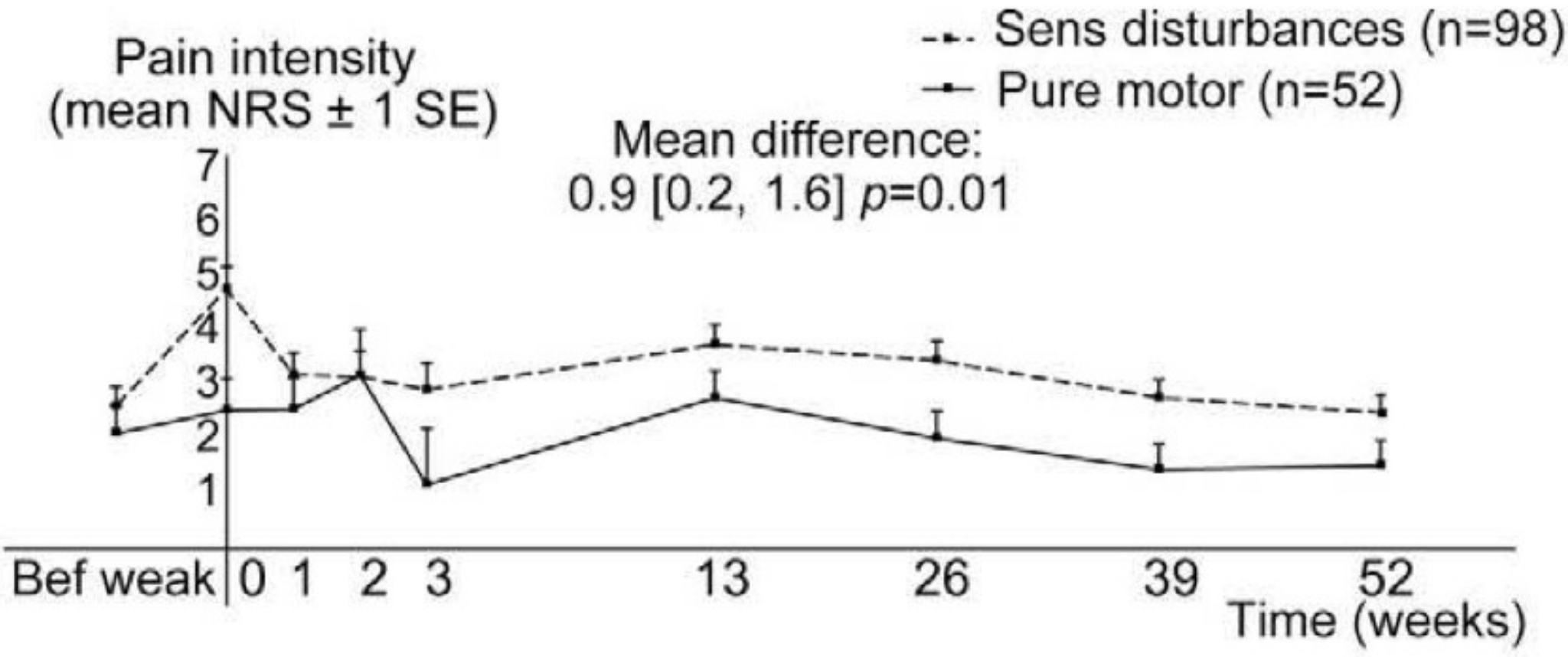
Table 2 Presence, location, severity, and interpretation of pain in GBS (n = 156) and the use of daily analgesics[a]

	Maximum 2 wk before onset of weakness	Acute phase[b]	13 wk	26 wk	39 wk	52 wk
Pain, n/N (%)	54/151 (36)	100/152 (66)	84/148 (57)	74/150 (49)	58/148 (39)	55/146 (38)
Severity of pain, n/n with pain (%)						
NRS 1-4	8/54 (15)	9/100 (9)	19/84 (23)	17/74 (23)	17/58 (29)	16/55 (29)
NRS 5-7	25/54 (46)	36/100 (36)	30/84 (36)	28/74 (38)	22/58 (38)	20/55 (36)
NRS 8-10	21/54 (39)	50/100 (50)	28/84 (33)	26/74 (35)	18/58 (31)	19/55 (35)
Unknown	0	5/100 (5)	7/84 (8)	3/74 (4)	1/58 (2)	0

Ruts et al. Neurology (2010) vol. 75 (16) pp. 1439-47

Ruts et al, 2010

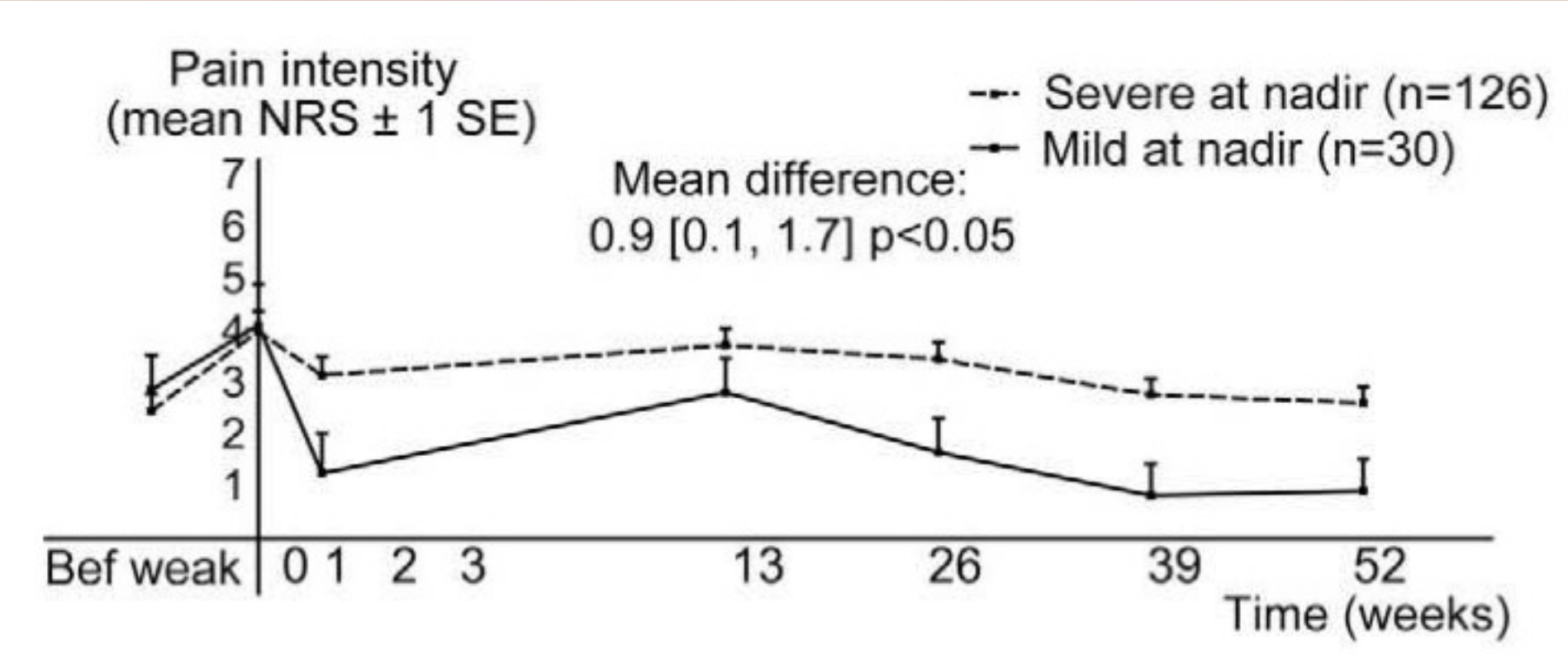
- When sensory disturbance was present, it was associated with more pain at all phases of follow-up



Ruts et al. Neurology (2010) vol. 75 (16) pp. 1439-47

Ruts et al, 2010

- More severe illness was associated with more pain
  (but pain still present in milder illness)
  - Mildly affected: able to walk unaided
  - Severely affected: unable to walk unaided



Ruts et al. Neurology (2010) vol. 75 (16) pp. 1439-47

Ruts et al, 2010

- The most common types of pain were myalgias in the low back or extremities, followed by radicular pain, and painful paresthesias/dysesthesias

	Acute phase[b]
Pain, n/N (%)	100/152 (66)
Locations of pain, n/n with pain (%)	
Low back or back	50/100 (50)
Interscapular	34/100 (34)
Extremities	76/100 (76)
Neck	34/100 (34)
Trunk	12/100 (12)

Interpretation of pain, n/n with pain (%)	
Radicular pain	31/100 (31)
Meningism	4/100 (4)
Painful paresthesias/ dysesthesias	43/100 (43)
Muscle pain	62/100 (62)
Arthralgia	14/100 (14)
Unknown	7/100 (7)

Ruts et al. Neurology (2010) vol. 75 (16) pp. 1439-47

Treating pain in GBS

- Little evidence for specific analgesics in GBS
- Only a single systematic review has made specific recommendations for treatment of pain in GBS (Hughes et al, 2005)
  - Simple analgesics or NSAIDs may be tried, but are often inadequate
  - Opioid analgesics may be used, with monitoring for side effects in the setting of autonomic denervation
  - TCAs and anti-epileptic drugs may have an adjuvant role
  - No discussion of steroids for treatment of pain

Hughes et al. Arch Neurol (2005) vol. 62 (8) pp. 1194-8

AEDs for treatment of pain in GBS

- Pandey et al (2002) studied gabapentin for the treatment of acute pain in severe GBS
  - 18 patients, admitted to ICU and ventilated
  - Cross-over design
  - Randomised to either placebo or gabapentin 15 mg/kg in three daily divided doses (approx 225mg NG tid on average) for seven days
  - Two day washout period, then
  - Seven days of treatment with the other modality
  - Fentanyl (2 mcg/kg) used as rescue analgesic

Pandey et al. Anesth Analg (2002) vol. 95 (6) pp. 1719-23

AEDs for treatment of pain in GBS

- Pain was recorded on numerical rating scale (NRS)
  - Scale from 0 – 10, 0 being no pain, and 10 the most severe
  - Patients reported NRS by eye blinks
- Significantly lower pain scores during all seven days of treatment with gabapentin, versus fentanyl only
  - Whether treated in the 1st or 2nd phase of the trial

Table 2. Pain Scores in Both Study Periods on Numeric Rating Scale of 0–10 (Mean ± SD)

	Day							
Variable	0	1	2	3	4	5	6	7
PTG (n = 18)	7.22 ± 0.83	3.48 ± 1.72*	2.33 ± 1.67*	2.20 ± 0.92*	2.04 ± 0.66*	2.14 ± 0.57*	2.10 ± 0.54*	2.06 ± 0.63*
PTP (n = 18)	7.83 ± 0.78	6.15 ± 1.02	5.76 ± 3.20	5.70 ± 0.98	5.72 ± 1.02	5.86 ± 0.76	5.70 ± 0.82	5.67 ± 0.91

PTG = period of treatment with gabapentin; PTP = period of treatment with placebo.
* $P < 0.001$, power of test >99%.

Pandey et al. Anesth Analg (2002) vol. 95 (6) pp. 1719-23

AEDs for treatment of pain in GBS

- Patients received rescue analgesia if NRS > 5 or if they requested additional treatment
  - Trained to demand analgesia by holding breath for >12 sec to trigger apnea alarm on ventilator
- Treatment with gabapentin significantly reduced opioid requirements
  - Maximal effect seen by day 2 of treatment

Table 4. Rescue Analgesic Consumption in Both Study Periods (μg) (Mean ± SD)

	Day						
Variable	1	2	3	4	5	6	7
PTG (n = 18)	211.11 ± 21.38*	68.05 ± 20.66*	63.89 ± 17.61*	70.83 ± 21.43*	68.05 ± 22.37*	61.11 ± 21.38*	65.55 ± 16.17*
PTP (n = 18)	319.44 ± 25.08	311.11 ± 21.38	319.44 ± 25.08	297.22 ± 36.26	305.56 ± 16.16	308.33 ± 25.75	316.67 ± 24.25

PTG = period of treatment with gabapentin; PTP = period of treatment with placebo.
* $P < 0.001$, power of test >99%.

Pandey et al. Anesth Analg (2002) vol. 95 (6) pp. 1719-23

AEDs for treatment of pain in GBS

- Adverse effects: sedation, GI symptoms
  - Increased sedation (Ramsay Sedation Scale) in both groups, but less in gabapentin group – probably due to decreased opioid use
  - Nausea in one gabapentin treated patient
  - 5 patients had nausea or constipation in the group treated with fentanyl alone

Table 3. Sedation Score in Both Study Periods on a Ramsay Sedation Scale of 1–6 (Mean ± SD)

	Day							
Variable	0	1	2	3	4	5	6	7
PTG (n = 18)	1.38 ± 0.50	2.15 ± 0.36*	2.38 ± 0.49*	2.45 ± 0.50*	2.48 ± 0.53*	2.47 ± 0.50*	2.51 ± 0.50*	2.44 ± 0.50*
PTP (n = 18)	1.44 ± 0.51	3.74 ± 0.44	3.56 ± 0.52	3.56 ± 0.50	3.62 ± 0.49	3.61 ± 0.50	3.70 ± 0.45	3.63 ± 0.51

PTG = period of treatment with gabapentin; PTP = period of treatment with placebo.
* $P < 0.001$, power of test >99%.

Pandey et al. Anesth Analg (2002) vol. 95 (6) pp. 1719-23

AEDs for treatment of pain in GBS

- Recent, larger study by Pandey et al has compared gabapentin, carbamazepine, and placebo
  - Enrolled GBS patients admitted to ICU over the course of 4 years
  - Total of 58 patients, 22 were excluded, 36 patients enrolled
  - Patients randomized to three equal sized groups:
    - Group one: gabapentin 300 mg tid
    - Group two: carbamazepine 100 mg tid
    - Group three: placebo

Pandey et al. Anesth Analg (2005) vol. 101 (1) pp. 220-225

AEDs for treatment of pain in GBS

- Pain recorded using NRS (via eye blinks)
- Rescue analgesia of fentanyl 2 mcg/kg
  - Demanded by triggering apnea alarm on ventilator
- Lower pain scores recorded in both treatment groups
  - pain scores lower in GBP group than CBZ group

Table 2. Pain Scores on a Numeric Pain Rating Scale of 0–10 (Median and Interquartile Range) in Different Groups

Group	0 h	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Gabapentin	8	3.5*	2.5*	2.0*	2.0*	2.0*	2.0*	2.0*
(n = 12)	(1.0)	(2.5)	(1.0)	(1.8)	(1.0)	(1.0)	(0.8)	(0.8)
Carbamazepine	8.0	6.0	6.0	5.0	4.0†	4.0†	3.5†	3.0†
(n = 12)	(1.0)	(0.8)	(0.0)	(1.0)	(0.8)	(1.0)	(1.0)	(1.0)
Placebo	8	6.0	6.0	6.0	6.0	6.0	6.0	6.0
(n = 12)	(1.0)	(1.0)	(0.8)	(1.8)	(1.8)	(1.8)	(1.8)	(1.8)

* $P < 0.05$ (gabapentin versus carbamazepine and placebo).
† $P < 0.05$ (carbamazepine versus placebo).

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AEDs for treatment of pain in GBS

- Treatment also associated with less fentanyl consumption
  - Which was also associated with lower sedation scores (again presumed due to less opioid use)
  - Less fentanyl use in GBP group than CBZ group
- No adverse effects recorded in this study

Table 4. Fentanyl Consumption in Different Groups (μg) (Mean ± SD)

Group	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Gabapentin	340.1 ± 34.3*	182.0 ± 28.6*	148.9 ± 27.6*	130.8 ± 31.4*	128.0 ± 32.4*	120.1 ± 26.4*	126.0 ± 26.2*
Carbamazepine	347.5 ± 38.0	277.5 ± 36.5†	212.0 ± 30.2†	198.5 ± 39.8†	180.5 ± 48.0†	174.5 ± 30.5†	174.5 ± 30.0†
Placebo	590.4 ± 35.0‡	421.1 ± 31.3‡	379.4 ± 36.0‡	348.2 ± 42.2‡	355.6 ± 28.1‡	368.3 ± 35.7‡	350.7 ± 34.2‡

Power of test, >90%.
* $P < 0.05$ (gabapentin versus placebo).
† $P < 0.05$ (gabapentin versus carbamazepine).
‡ $P < 0.05$ (carbamazepine versus placebo).

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AEDs for treatment of pain in GBS

- A smaller study of carbamazepine had also found reduction of pain, again in the ICU setting (Tripathi and Kaushik, 2000)
  - Enrolled 12 ventilated patients
  - Crossover design; patients received 3 days of treatment (CBZ 100mg q8h) or placebo, 1 day of washout, then 3 days of the opposite regimen
  - Rescue analgesia with pethidine (meperidine)
  - There was reduction of pain scores and pethidine usage during the days of treatment with CBZ

Tripathi and Kaushik. Crit Care Med (2000) vol. 28 (3) pp. 655-8

AEDs for treatment of pain in GBS

- Single case report of CBZ 400mg qhs for pain:
  - "There seems little doubt that tegretol relieved the severe pain associated with Guillain-Barré syndrome in this patient." (Winspur, 1970)
  - The patient was also given prednisone 60mg daily
- Five patients received CBZ for adjuvant analgesia in a prospective study of pain in GBS patients
  - "Pain relief gradually improved with analgesic intervention..." (Moulin, 1997)
  - No comparison of analgesics (acetaminophen, NSAIDs, opioids, TCAs, quinine, CBZ) used

Winspur. Lancet (1970) vol. 1 (7637) pp. 85 Moulin et al. Neurology (1997) vol. 48 (2) pp. 328-31

AEDs - Conclusions

- Three small studies from the anesthesiology and critical care literature support the use of gabapentin and carbamazepine
  - For ventilated ICU patients, ie severe GBS
  - Results included reduction of pain scores, and decreased use of opioids
- Data is lacking regarding use AEDs in mild to moderately affected GBS patients, but it would seem to be a reasonable choice to reduce opioid use
  - Most data is anecdotal or descriptive

Steroids for treatment of pain in GBS

- Steroids have been used for treatment of motor symptoms of GBS and may have analgesic effects
  - Reduction of perineural and endoneural inflammation?
- Case reports suggest reduction of pain in GBS
  - Two patients improved with IM methylprednisolone (Ropper and Shahani, 1984)
  - Improvement of back pain with methylprednisolone in one patient (Sánchez-Guerra et al, 2002)
  - Four patients had relief of pain with corticosteroids (Kabore et al, 2004)

Steroids for treatment of pain in GBS

- One larger study (Ruts et al, 2007) has retrospectively reviewed analgesic properties of methylprednisolone in GBS patients
  - Patient data was extracted from a double-blind RCT of IVIg vs IVIg + Methylprednisolone for treatment of GBS (van Koningsveld et al, 2004)
  - Primary endpoint in the original study was improvement of GBS disability score
  - Of 225 patients enrolled, 123 had pain at time of randomisation

Ruts et al. J Neurol (2007) vol. 254 (10) pp. 1318-22

Steroids for treatment of pain in GBS

- Ruts et al compared the prevalence of pain between the IVIg/Placebo and IVIg/MP groups
- There was no significant difference among groups in frequency, improvement, or deterioration of pain.

	IVIg/Placebo group (n = 112)	IVIg/MP group (n = 111)
Patients with pain (n, (%))		
Randomization	67 (60)	56 (50)
4 weeks after randomization	58 (57)	51 (49)
Patients with a decrease in pain severity (n, (%))		
4 weeks after randomization	34 (34)	32 (31)
Patients with an increase in pain severity (n, (%))		
4 weeks after randomization	26 (26)	22 (21)

MP = methylprednisolone

Ruts et al. J Neurol (2007) vol. 254 (10) pp. 1318-22

Steroids - Conclusions

- Case reports suggest good analgesic response to steroid therapy
- However, the only larger (but retrospective) study to date failed to show any analgesic benefit of corticosteroids

Opioids for treatment of pain in GBS

- Opioid analgesia is frequently described as effective for treatment of pain in GBS
  - IV or PO routes
  - Morphine, oxycodone, fentanyl, meperidine, have all been used
  - Higher doses used in ICU/ventilated patients (remifentanil infusion in a single patient)
- Epidural opioid analgesia has been reported to be effective for severe, refractory pain in GBS
  - Total of twelve patients described

Opioids for treatment of pain in GBS

- Genis et al (1989) reported a series of 9 GBS patients who were treated with epidural morphine
  - 2 patients were ventilated
  - All had severe pain that prevented sleep
  - Not controlled with “routine” analgesics
  - Pain control: “total” in 7 patients, good in 1 patient, slight in 1 patient
  - Adverse effects included catheter displacement (4 patients), urinary retention, pruritus, nausea, vomiting

Genis et al. J Neurol Neurosurg Psychiatr (1989) vol. 52 (8) pp. 999-1001

Opioids for treatment of pain in GBS

- Three other reports of epidural analgesia for GBS:
  - Original case report – 20M treated with epidural morphine infusion for ten days (Rosenfeld et al, 1986)
  - 34F treated with epidural fentanyl infusion (later epidural morphine) for 37 days, after failing to respond to carbamazepine and phenytoin (Connelly et al, 1990)
  - 40F treated with epidural fentanyl/bupivicaine (for a total 22 days) with good response (Ali et al, 1992)

Opioids - Conclusions

- Opioid analgesics are frequently used for the treatment of pain in GBS
- They appear to be effective, though this has not been quantified by prospective studies
- There is a concern of increased opioid-related adverse effects (sedation, ileus, respiratory depression) in patients with immobility, respiratory compromise, or autonomic denervation
- Epidural opioids are an option for severe, refractory pain.

Non-pharmacological approaches

- To date, there have been no studies of non-pharmacological management (exercise, physiotherapy, massage, etc) of pain in GBS
  - Case reports of epidural analgesia reported failure of transcutaneous electrical nerve stimulator to improve symptoms
- One study (Garrssen et al, 2004) did report improvement of self-reported fatigue scores in 16 GBS patients (post-recovery) following a 12-week program of stationary cycling

Take home points

- Sensory disturbance and pain are common in the initial presentation of GBS
  - Sensory symptoms may precede motor symptoms and introduce diagnostic confusion
- Pain is common in the acute phase
  - It is often severe
  - It responds to treatment, but there isn't much evidence for specific drugs
- Pain may persist in later phases and contribute to functional disability

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