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Evaluation of prednisolone treatment in the acute phase of neuralgic
amyotrophy: An observational study

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Abstract:

Introduction: Effective treatment for neuralgic amyotrophy (NA), a disabling brachial plexus syndrome of supposed immuno-mediated origin, is currently lacking. Given the circumstantial evidence of a beneficial effect of prednisolone on pain and paresis, this report evaluates the effects of prednisolone treatment administered in the acute phase in a retrospective case series of 50 NA patients. **Methods:** Baseline variables (e.g. age, sex, type of NA, and number of attacks), treatment variables (e.g. time until treatment, regimen, and use of analgesics), and outcome measures (e.g. duration and severity of pain, time course and severity of paresis, and functional outcome) were statistically analyzed and compared to an historical control group of 203 untreated NA patients. **Results:** The baseline characteristics of the two patient groups were comparable. Median time until initial pain relief was lower in the study group (12.5 days vs. 20.5 days) and a significantly higher percentage already recovered strength in the first month of treatment (18% vs. 6.3 %; $p=0.011$). Twelve percent had fully recovered within one year while this was 1% for the controls ($p<0.001$), with the proportion reporting a 'good' 12-month outcome also being higher (44% vs. 10.7 %; $p<0.001$). Side effects were reported by 20%, but none led to a discontinuation of treatment. **Conclusion:** Oral prednisolone seems effective in the acute phase of neuralgic amyotrophy with the current results supporting previous case reports. A regimen of oral prednisolone is therefore recommended in the acute phase of the syndrome pending a prospective, randomized trial verifying the results obtained.

Introduction

Neuralgic amyotrophy (NA) is clinically characterized by attacks of acute and severe (neuropathic) pain in shoulders and arms, followed by a patchy paresis after days or weeks due to axonal damage of the brachial plexus. The minimum annual incidence of NA is 2-to-3 per 100,000, but this might be an underestimation.[1] An idiopathic variant (INA) with a generally monophasic course and an autosomal dominant hereditary variant (HNA) with recurrent attacks exist. The initial pain lasts three weeks on average. Paresis is usually moderate to severe, but varies between patients and affected muscles. In 70% of the patients the upper trunk of the brachial plexus is involved. Both INA and HNA are self-limiting and generally show a moderate to good recovery. However, after three years 75% of the patients still report pain and residual paresis and 25% are still unable to work. These numbers underscore the need for effective treatment strategies, which, to date, are lacking.

[1]

Neuralgic amyotrophy is assumed to have a complex aetiology, in which autoimmune, mechanical and genetic factors appear to play a role.[2] Observations that symptoms are often (25-40%) preceded by an antecedent infection, or sometimes by a vaccination or immunomodulating treatment (such as interleukin 2 or interferon alpha 2) support the notion that attacks are immunomediated, explaining the term "immune-mediated brachial plexopathy" some authors prefer.[3,4] Accordingly, attempts have also been made to treat patients with immunomodulatory medication, with several case reports and small-scale case series indicating that in some patients treatment with corticosteroids might be effective.

[1,3, 5-20] None of the regimens have, however, been systematically evaluated in significant numbers of patients. In our institute, the national referral centre for NA in the Netherlands, prednisolone treatment was empirically initiated for patients in the early stages of their

disease while they were still suffering from severe pain either with or without conventional analgesic measures. Although due to the lengthy, but common, delays in the diagnosis (median 10.7 weeks), treatment with prednisolone was relatively infrequent, we can now report the first effects of open-label treatment with oral corticosteroids in a retrospective series of 50 NA patients that were treated within one month of attack onset.

Methods

Patients and clinical criteria

We reviewed the charts of all NA patients seen at our Neuromuscular Centre from September 2000 until September 2007 and selected any patient with a well-documented attack of acute severe shoulder and/or arm pain followed by paresis within days to weeks in whom other diagnoses than NA were excluded and who was treated with corticosteroids within 1 month (31 days). Note that the study cohort (n=50) also included 16 patients whose clinical details were described earlier.[1] For the NA diagnoses we adopted the modified HNA criteria by Hannibal et al. in that we did not consider family history.[21] The clinical diagnosis was supported by EMG, and an MRI of the cervical spine was performed to exclude degenerative pathology as a cause of symptoms when necessary. If patients had suffered more than one attack, the first attack treated was used for further analysis. We recorded age, sex, type of NA, number of attacks, severity of the initial pain and of the initial paresis, attack side, and antecedent events with special attention to antecedent infections because of their possible role in the presumed autoimmune pathogenesis of NA.[2] Because the extent and severity of the paresis can vary considerably between patients, paresis severity was quantified as an MRC (Medical Research Council) sum score (range 0-15), which is the sum of the MRC scores (range 0-5) of the three weakest muscles for each patient. To put our data into perspective, we compared the recovery data of our treatment group to the data of 203 untreated NA patients seen during the same period.

Treatment variables

The time until treatment, treatment regimen, use of analgesics and timing of analgesic use were recorded. The standard regimen comprised a 13-day course of oral prednisolone 60

mg/day in the first week, tapered by 10 mg every day during the next five days, ending with 5 mg on day 13. Alternative dosing regimens and schedules were also noted. The time until prednisolone treatment was defined as the number of days between the start of the pain and the start of prednisolone. Side effects of the corticosteroid were noted, as was the use of both NSAIDs and opiates, with opiate use being further classified as occurring before, simultaneous with, or following prednisolone treatment.

Outcome measures

Because of the variability in the follow-up (FU; see Figures 1a and 1b), it was decided to take the clinical follow-up date closest to six weeks after treatment initiation as FU1 to allow the detection of early differences in recovery of paresis and functional outcomes, which during the natural course of the disorder usually manifest themselves within this time window. To identify differences in overall functional recovery, the last follow-up date available was adopted as FU2.

The chart-derived outcome measures included: duration and severity of pain, time course and severity of paresis, duration and time to amelioration of pain and/or recovery of strength, self-reported functional outcome and treatment effect, recurrence of pain after treatment, and side effects at FU1 and FU2. Patients rated pain using a 11-point numerical rating scale (NRS (0-10), ranging from 'No pain' to 'Most severe pain imaginable'). Duration of the initial pain period (defined as the time in days for the NRS score to decrease at least 2 points after the start of the symptoms) was recorded and classified in five categories: within 24 hours, between 1-7 days, 1-2 weeks, 2-4 weeks, and >4 weeks.

Recovery was assessed using several parameters: (1) strength at FU2 was evaluated based on the MRC sum scores of the three weakest muscles, with sum-scores of ≤ 10

signifying severe paresis, 11-13 moderate paresis, and 14-15 mild or no paresis; (2) the time course of the paresis, with the first recovery of strength being classified as having occurred within 2 weeks, 2-4 weeks, 1-6 months, or >6 months; and (3) subjective improvement of strength at FU1 rated using a 5-point scale: no improvement, 25%, 50%, 75% improvement, and full recovery.

Patients rated their functional recovery at FU1 and FU2 using a 4-point scale: hardly any, moderate, good, or full recovery. To optimize comparability of the outcomes of our two patient groups, we compared the patients' FU1 outcomes to the outcomes the historical controls had reported during an evaluation until one year after their initial NA attack, while FU2 outcomes were contrasted with the controls' outcomes obtained during the last evaluation date available.

Statistical analysis

Statistical analyses were performed using SPSS 12.0.1 software (SPSS Inc., Chicago, Illinois, USA). For each variable, the number of cases was recorded and percentages calculated, which, in case of missing data, were based on the number of available cases.

Pearson's Chi-square test (2-sided, with significance set at ≤ 0.05) was used to compare subgroups with categorical variables. Student t-tests were used to compare subgroups with continuous variables. Linear regression with a forward selection procedure was performed to determine which patient, attack and treatment variables independently predicted functional recovery at FU1 and FU2. Differences in initial-pain duration between the open-label group and the historical controls were computed using a Mann-Whitney U test (2-sided) because of non-Gaussian distribution of this variable in both groups.

Results

Patient and clinical data

The characteristics of the patients and the controls, and attack features, where available, are shown in Table 1.

Table 1. Patient characteristics of the study (prednisolone) group (SG) and the historical (untreated) controls (HC) and attack characteristics for the study group.

Demographics		SG (n=50)	HC (n=203)	
Sex, male (%)		30 (60%)	141 (69.5%)	NS
Idiopathic NA, number (%)		38 (76%)	166 (81.8%)	NS
Age, median (range)		45,5 (22-74)	45.7 (12-83)	NS
Mean number of attacks		1.5 (1-16)	1.7 (1-13)	
Number of recurrent attacks (%)		26 (52%)	70 (34.5%)	<i>p=0.034</i>
Attack side	Left	21 (42%)	51 (25.1%)	
	Right	18 (36%)	95 (46.8%)	
	Bilateral	11 (22%)	57 (28.1%)	
Initial pain (NRS [*]), mean (range)		9 (5-10)	9 (5-10)	
	NRS 5-7	9 (20%)	21 (16.7%)	
	NRS 8-10	36 (80%)	105 (82.3%)	NS
	Missing values	5	77	
Initial strength [§]	Mean MRC sum score	10 (2-15)	n.a.	
	Sum score ≤ 10 and MRC < 3	23 (48.9%)	128 (66.7%)	NS (<i>p=0.08</i>)
	Sum score 11-13 and MRC 3-4	17 (36.1%)	42 (21.9%)	
	Sum score 14-15 and MRC 4-5	7 (14.9%)	22 (11.5%)	
	Missing values	3	11	
Antecedent event		20 (40%)	98 (48.3%)	NS
Antecedent infection		9 (18%)	43 (21.2%)	
Time to prednisolone, mean (range)		8.5 (1-31)	-	
Standard treatment		43 (86%)	-	
Analgesics		27 (54%)	116 (57.1%)	NS
NSAIDs	Number of (%)	8 (16%)	71 (35%)	<i>p=0.001</i>
Opiates	Overall use	21 (42%)	45 (38.8%)	NS
	Start before prednisolone	9 (18%)	-	
	Start during prednisolone	7 (14%)	-	
	Start after prednisolone	2 (4%)	-	
	Timing unclear	3 (6%)	-	

* NRS numerical rating scale; § Mean and range of MRC sum score for the SG and MRC for the HCs; n.a. not available

As expected, in the study group the initial pain as rated with the NRS was severe, with 36 of 45 (80%) patients reporting scores of 8-10 and the other nine (20%) scores of 5-7. Of the nine patients that took opiates prior to prednisolone treatment, two still had scores of 5-7

and six even scores of 8-10. Of the three patients with missing NRS scores one had characterized his pain as 'severe'. Based on the MRC sum scores of 47 patients, paresis was severe (<10) in 23 (48.9%), moderate (11-13) in 17 (36.1%) and mild (14-15) in seven patients (14.9%). One patient had an attack that was initially restricted to pain but within two weeks of treatment developed a severe paresis.

As to the differences in baseline characteristics of the two patient groups (Table 2), the prednisolone group included more patients having experienced recurrent attacks (52.0% vs. 34.5%, $p=0.034$), more female patients (40.0% vs. 30.5%, $p=0.24$) and more patients with HNA (24% vs. 17.2%, $p=0.39$), whereas the control group comprised a higher percentage of patients with severe paresis (67% vs. 52%, $p=0.08$).

Treatment regimens

The median time between the initial symptoms and the start of prednisolone treatment was 8.5 days (range 1-31), with 18 patients (36%) being treated within one week, 21 (42%) from the second week, and 11 (22%) after two to four weeks. Forty-three patients (86%) followed the standard 13-week regimen, while seven (14%) had had alternative doses or schedules. Of these, two patients completed the standard regimen but were then prescribed a four-week continuation treatment of 5 mg/day oral prednisolone. One patient received a 3-week course (with 60 mg/day for two weeks), another 60 mg of prednisolone for six rather than seven days, and a third 50 mg of prednisolone for five days before tapering. A fourth patient tapered the 60 mg start dose in two rather than seven days, and the fifth took 60 mg/day for one week, then 45 mg/day and 30 mg/day each for one week before tapering in two weeks. Ten patients (20%) reported side effects of the prednisolone, i.e., mood swings ($n=7$; 14%) and gastrointestinal complaints ($n=3$; 6%), but none chose to stop treatment because of

these symptoms. Treatment was rated as effective by 44 patients (88%), while six patients (12%), of whom three had suffered a recurrent attack, felt that prednisolone had had no effect.

In the treatment group, 21 patients (42%) had been prescribed opiates, nine of whom (18%) before initiation of prednisolone treatment (without sufficient relief); seven (14%) had started taking opiates during and two (4%) after discontinuation of prednisolone treatment. The opiate regimens of three patients could not be retrieved. Opiate use was slightly but non-significantly lower in the control population (38.8% vs. 42%, $p=0.70$), while the consumption of NSAIDs was significantly lower in the prednisolone group (16% vs. 35%, $p=0.01$). The information on the duration of analgesic treatment was insufficient for analysis.

Treatment outcomes

The median FU1 was 47.0 days (9-350) and the median FU2 132.5 days (9-665); distributions are shown in Figures 1a and 1b. The outlier was a patient first seen at our outpatient clinic for a second opinion after 350 days following his NA attack; the data for the preceding period were insufficiently available to classify FU1 any earlier. For 34 (68%) patients the last follow up available (FU2) was at least 12 weeks since disease onset.

Pain

Nine patients (18%) experienced pain relief within 24 hours after the first dose of prednisolone and 25 patients (50%) after two to seven days. The median interval between pain relief and treatment onset was 2.5 days (mean 7.4, SD 11.6; range 1-60), with the median time between pain relief and the onset of the complaints totalling 12.5 days (mean 17.0, SD 13.8; range: 3-69). Eleven patients (22%) reported a return of the initial neuropathic

pain after discontinuing prednisolone treatment. The median time until pain relief in the untreated control group was 20.5 days (mean 37.2 days, SD 67.7 ; range: 1-365). Differences in disease course are summarized in Table 2.

Paresis

Seven patients (14%) reported improvement of their strength within two weeks after the start of prednisolone treatment, two (4%) within two to four weeks, 27 (54%) after one to six months, and 14 patients (28%) not until six months had passed. In the control group, 6.3% had started to recover within four weeks, 53.4% within one and six months, and 40.2% after six months. The group difference in early recovery (18% vs. 6.3%) was statistically significant ($p=0.011$). At FU1 a median of 25% reported improvement of strength. Fifteen (30%) treated patients reported improvements of 50% or more, of whom two claimed full recovery of strength, 22 (44%) patients experienced a 25% improvement, while 13 patients (26%) felt they had no improvement. The subjective ratings were confirmed by physical examination as reflected by improved MRC sum scores in 33 of 47 patients (70%). Ten patients (20%) reported progression of the paresis during treatment, of whom four had regained strength at FU1, while the other seven patients had not noticed any improvement until after six months.

Functional outcome

At FU1 three treated patients (6%) indicated to have had a full functional recovery, 11 (22%) a good and 21 patients (42%) a moderate recovery, while 15 patients (30%) reported to have hardly noticed any improvement. At FU2 the numbers were six (12%), 20 (40%), 20 (40%), and four (8%), respectively.

A significantly higher percentage of patients in the prednisolone group recovered fully within one year compared to the untreated controls (12% vs. 1%; $p=0.000$), which also holds for those patients reporting a good outcome within six (32% vs. 2.9%; $p=0.000$) and within 12 months (44% vs. 10.7%; $p=0.000$; see Table 2).

No differences in the baseline variables were found between the treated patients that recovered quickly and those that recovered later, but the fully recovered patients had started taking prednisolone significantly earlier (on average, 6.2 days vs. 10.7 days; $p=0.027$).

Table 2. Outcomes for the study (prednisolone) group (SG) and the historical controls (HC)

	SG	HC	
Median time until initial pain relief in days (mean)	12.5 (17.1)	20.5 (37.2)	<i>ns, $p=0.13$</i>
Recovery of strength within 1 month	9/50 (18.0%)	11/174 (6.3%)	<i>$p=0.011$</i>
Full functional recovery within the first year	6/50 (12.0%)	2/189 (1.0%)	<i>$p<0.001$</i>
Good (but not full) self-reported recovery within -6 months	16/50 (32%)	3/103 (2.9%)	<i>$p<0.001$</i>
-12 months	22/50 (44.0%)	11/103 (10.7%)	<i>$p<0.001$</i>

Subgroup analysis

The patients with recurrent attacks started to recover significantly later than those that were treated for a first attack. This was reflected in the proportion of patients whose MRC sum scores had risen at FU1 (recurrent 13/25 vs. non-recurrent 20/22; $p=0.004$), in the ratios that recovered strength later (i.e., after six months; recurrent 8/18 vs. non-recurrent 1/21; $p=0.017$) and those that reported little or no recovery at FU2 (recurrent 12/26 vs. non-recurrent 1/24, $p=0.001$). Moreover, at FU2 a larger proportion of patients with recurrent attacks reported no more than moderate recovery (14/26 vs. 6/24, $p=0.038$). Linear regression confirmed that recurrent illness independently predicted poorer functional outcome at FU2.

Patients reporting an antecedent infection recovered earlier (proportion of full recovery at FU1: 2/9 vs. 1/41; $p=0.024$) and more often fully (full recovery at FU2: 3/9 vs. 3/41; $p=0.030$), but the regression model did not show this effect to be independent of type of NA, sex, and the time until prednisolone treatment. Duration until amelioration of the pain didn't differ significantly between the patients with and without antecedent infections nor for the presence or absence of antecedents in general. None of the subgroups showed a significant difference in follow-up duration (FU1 and FU2).

In the regression model poorer functional outcome at FU1 in the prednisolone group was independently predicted by the presence of HNA, by a recurrent illness and by severe initial paresis (MRC sum score <10). Poorer functional outcome at FU2 was predicted by a recurrent attack only. Analyses did not reveal a particular subgroup that predicted a better outcome with prednisolone.

Discussion

The results of our observational study show that corticosteroid treatment in the early stages of an NA attack can positively affect outcome. First, relative to the untreated patients, a significantly higher proportion of the patients receiving oral prednisolone recovered early from their pareses. Second, taken in the first month, prednisolone decreased the average duration of the initial pain, which was 20.5 days in the historical controls and 12.5 days in our study group. Although not statistically significant in our series, such a difference clearly has clinical relevance. Thirdly, functional recovery set in earlier, with significantly more treated patients achieving full recovery within a year or reporting a 'good' outcome within six months. Finally, although side effects occurred in 20% of our patients, they were never a reason to discontinue treatment.

Our case series comprised more patients with HNA and more patients with recurrences (to which HNA patients are also more prone), suggesting that timely treatment was more common in these types of patients in whom NA is recognized more easily and hence earlier, both by the patients themselves and health professionals. However, high proportions of recurrences may result in an underestimation of the potential treatment effect of prednisolone on paresis and functional recovery, because patients with recurrences are known to do worse, probably because of residual damage incurred during previous attacks.[1] Indeed, recurrent attacks independently predicted a poorer outcome in this study.

Proportionally, more patients with a reported antecedent infection eventually recovered fully after prednisolone treatment, although the antecedent event did not independently contribute to the outcome. No significant correlation between the time until treatment and outcome was found for the group as a whole, which suggests that treatment

can be effective when started anytime within four weeks of attack onset. Still, all six patients reporting a rapid and full recovery had been treated within ten days after the first symptoms, i.e., significantly earlier than the patients reporting partial recovery, which underscores that earlier treatment is more likely to yield better results.

Although based on case reports and small, uncontrolled case series only, available evidence suggests that outcomes in patients with NA can be improved through immunosuppressive agents. [1,3, 5-20] Even though the aetiology is unclear, we hypothesize that an immunomediated response causing NA might be B cell-mediated (molecular mimicry) due to the postinfectious nature, or T cell-mediated due to findings of activated brachial plexus T-cell clones.[22] Prednisolone suppresses cellular as well as humoral immunity when given in high doses. Evidence in the available literature shows anecdotal effects of IVIG, methylprednisolone or ACTH on neuralgic amyotrophy that are comparable to those found for prednisolone. [1,3,5-20]

It should be noted that our study is likely to be biased because of its retrospective, non-blinded nature. In the absence of a random allocation to treatment groups, the results may have been confounded by indication.[23] Moreover, although our two patient groups were largely comparable, the higher percentage of patients with a severe initial paresis in the control group may have inflated the prednisolone effect. Paresis is known to progress in about a third of all patients as part of the natural course of the disease.[1] Possibly, some of the patients were seen and subsequently treated in an early phase when paresis was not yet full-blown but still progressing. Furthermore, the overrepresentation of male patients - who are known to report pain as more intense - in the control group might have skewed results in favour of prednisolone. The concomitant use of analgesics might have affected the outcomes. Most likely the elevated use of NSAIDs in the controls skewed results against

prednisolone treatment. One could also hypothesize that decreased need for NSAIDs in the study group is an effect of prednisolone treatment on pain. Despite the fact that in the majority of cases the clinical follow-ups were performed by one of the authors (NvA), we were still confronted with missing data, hampering our regression analyses and possibly generating suboptimal results. However, we cannot predict the direction of this potential bias. The prednisolone treatment may also have been suboptimal. Specifically, the recurrence of the primary neuropathic pain in 22% of the patients after discontinuing prednisolone suggests that our treatment schedule was too short for some, while paresis progression during treatment, occurring in a fifth of the patients, also suggests that steroid treatment may have been insufficient. Finally, our series may have been too small to identify subgroups of patients that might differ in terms of treatment benefit. It is plausible that there are several pathophysiological mechanisms underlying what we currently define as 'NA', and in some patients mechanisms may not be steroid-responsive at all.

Despite these limitations and pending supporting evidence, we feel justified in recommending prednisolone, in the absence of contraindications, in the early treatment of patients with acute neuralgic amyotrophy. It should preferably be given at the earliest opportunity following an attack. As not all patients will respond favourably, the effect has to be weighed carefully against any side effects. Because of their tentative nature, our results did stress the need for a prospective, double-blind, randomized trial with oral prednisolone, which is in progress at our centre.

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