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Neuropathy in eosinophilic granulomatosis with polyangiitis: a comparison study of 24 cases with or without prior leukotriene antagonist exposure

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Summary

Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome (CSS), is a systemic vasculitis affecting almost exclusively patients with asthma. Neuropathy is the presenting feature in 55-75 % of cases. An increased incidence of the syndrome has been reported in asthmatics treated with leukotriene antagonists (LTAs). The causal relation is still debated. We retrospectively examined clinical, biochemical, histological features, and outcome of patients referred between 1990 and 2006 for sural nerve biopsy affected by neuropathy related to EGPA.

We identified 24 patients, 6 treated with LTA montelukast (T-group) and 18 not treated (NT-Group). All had chronic asthma; in T-group neuropathy developed from 1 to 150 days after starting montelukast. Demographic features as well as asthma duration and pre-onset treatment were remarkably similar, with the only exception of a statistically nonsignificant larger involvement of the nasal mucosa in T group. Nerve biopsy revealed in both group an axonal neuropathy. At follow-up, all within the T-group and most within the NT-group improved clinically; neurophysiological parameters remained stable, improved or worsened in the same proportion within the two groups.

Only 2 NT and no T-patient had stopped steroid treatment before the appearance of the peripheral neuropathy, making withdrawal overall unlikely as a causative factor of the onset of neuropathy. In summary, the temporal relationship between montelukast administration and the onset of neuropathy, would make the latter more likely as an "adverse drug reaction". Despite this, no significant clinical neither neurophysiological differences were noted between the two groups.

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare idiopathic systemic necrotizing vasculitis described in 1951 in patients with chronic asthma who developed a pathological picture characterized by peripheral eosinophilia and granulomatous vasculitis of small and medium size vessels (1). Since the first description, this syndrome has been reported in patients without asthma, but with a much lower prevalence (2,3). The pathogenesis of EGPA remains still debated. A major role has been attributed in the past to withdraw of oral or inhaled steroids in asthmatic patients, that can unmask "forme fruste" of this syndrome following the addition of new drugs such LTI. Despite these observations, steroid withdraw cannot be considered the only triggering factor, as the syndrome has been described also in non asthmatic patients (2,3), in asthmatic patients not taking steroids (16,19), and after administration of several medications as LTAs (11,12,13,14,15,16,17,18).

According to the American College of Rheumatology criteria (4), this syndrome is diagnosed if at least 4 out of the following 6 items are present: 1) asthma; 2) peripheral eosinophils more

than 10% of white blood cell count; 3) non-fixed pulmonary infiltrates; 4) polyneuropathy or mononeuropathy; 5) paranasal sinus abnormality; 6) extra vascular eosinophils on tissue biopsy. Peripheral nervous system involvement in EGPA has been reported in 55-75% of cases, according to the series reported by Hattori (5) and Sehgal (6), and is often present at the onset of disease (7). Mononeuropathy multiplex is the most frequent pattern (it is found in 71% of patients) whereas polyneuropathy is relatively rare (29% of cases) (5).

The incidence of EGPA in general population varies from 1,8 to 3,3 cases/million/year (9). In the asthmatic population not receiving LTAs is 60 cases/million asthmatic/year (8,9). Since the advent of leukotriene antagonists (LTAs) in 1998, the incidence seems to have increased (10). All LTAs have been considered as possible triggers of this syndrome (11,12, 13,14,15,16,17,18,19).

A later population based study did not confirm the increased incidence reported previously (20). So far, just small series of patients who developed neuropathy as a sign of EGPA following the treatment with LTAs have been described in detail.

The aim of this study is to compare the peripheral involvement in patients with EGPA treated with LTAs to that in patients not treated with LTAs, and to assess whether there are differences in the neurological clinical presentation, in the neuropathological picture and in neuropathy outcome.

Material and methods

We reviewed all nerve biopsies performed in the Neuropathology Unit of the Department of Neurology of the University of Verona between 1990 and 2006. Of these, we identified the cases referred with neuropathy associated with eosinophilic granulomatosis with polyangiitis. Past medical history was obtained by reviewing medical notes. The following investigations were available: 1) full blood count and erythrosedimentation rate; 2) anti-neutrophil cytoplasm antibodies with a perinuclear pattern (pANCA); 3) chest x-ray; 4) nerve conductions studies (NCS). For some patients, results of bronchoalveolar fluid analysis, skin and muscle biopsies were also available.

Nerve conduction studies were performed in all patients according to methods described by Kimura (21). Sural nerve biopsies, performed after obtaining informed consent, were divided into three portions and processed as previously described (22). In brief, one portion was fixed in 4% paraformaldehyde, embedded in paraffin, and stained with haematoxylin-eosin; the second portion was fixed in 2.5% glutaraldehyde, embedded in epoxy resin and processed for light and electron microscopy; teased fibres were also obtained; the third portion was frozen for cryosections.

The inflammatory infiltrates were characterized by immunocytochemistry with anti-CD20 (recognizing B-lymphocyte), CD45Ro (T-cell) and anti-CD68 (macrophage) antibodies (Dako, Glostrup, Denmark) (22). Abnormalities of sural nerve biopsy were obtained by two independent neuropathologists.

Clinical and neurophysiological follow-up of each patient were performed in the referring centres. Clinical outcome was assessed by the change of the MRC score from the first to the last available neurological follow-up. Neurophysiological outcome was graded as stable (no changes in the amplitudes of compound sensory [cSAP] or motor [cMAP] action potential, or in nerve conduction velocity [NCV], or changes within normal variance), improved (increase > 20% of the amplitude of cSAP or cMAP), worsened (decrease of > 20% of the amplitude of cSAP or cMAP) or evolution to a polyneuropathy.

The patients were divided into two groups (treated or "T-group" and not treated or "NT-group"), according to whether or not they had received montelukast prior to clinical onset of neuropathy. The two groups were compared in terms of demographic and clinicopathological features, response to treatment, clinical and neurophysiological outcome. T-test with correction for multiple comparisons was used to compare normally distributed variables, and Fisher's exact test was used to compare frequencies.

Results

Clinical, laboratory and neurophysiological features

The general characteristics of the patients and the principal data of past medical history are reported in **table 1** and **2**. Twenty-four patients affected with asthma were referred to our Department after the onset of neuropathy, for diagnostic nerve biopsy. None of the patients had other possible causes of neuropathy. Six out of the 24 patients received, as therapy for asthma, montelukast (10 mg once a day) 1 to 150 days before the onset of neuropathy; in none of these patients had steroids been withdrawn, whereas in the NT group this had occurred in 2/18 (12%) patients. As for steroids, all treated patients where under inhaled steroid, while in the non-treated group three (case 1-4-5) where taking oral steroids, the others inhaled steroid. Only in one patient eosinophilia > 10% was present before neuropathy onset (this patient suffered of an hypereosinophilic syndrome). pANCA were available in 21 patients: they were positive in 3/6 (50%) within the T-group and in 6/15 (40%) within the NT-group (p = 0,523). Nasal polyposis was present in 7/18 (39%) patients within the NT group and in 5/6 (83%) within the T group, but the difference failed to reach statistical significance (p = 0,077). Radiographic chest involvement was present in 4/6 (66%) patients within the T group and in 7/16 (44%) patients within the NT group, with non-statistical difference (p = 0,635). Neurological symptoms at onset and neurophysiological findings are reported in **table 3**. Peripheral nerve involvement

presented with a mononeuropathy multiplex in 6/6 (100%) patients within the T-group, and in 15/18 (83%) in the NT-group (p = 0,285); in the remaining 3 (17%) a polyneuropathy was the pattern of nerve involvement. Upper and lower limbs were affected in both groups without any difference. Exclusive upper limb involvement was only observed in 3/18 (17%) of NT patients. Nerve conduction studies performed on admission revealed an axonal involvement in all patients and no signs of demyelination. In both groups, a sensorimotor or mainly motor involvement was dominant, while a pure or mainly sensory neuropathy was present only in 1 patient within the NT-group. In MM with a mainly motor involvement, sural nerve amplitude was not always absent but reduced, often in asymmetric pattern.

Sural nerve biopsy

Pathological findings of nerve biopsy are summarized in **table 4**. Sections stained with haematoxylin and eosin, revealed signs of vasculitis (either epineurial inflammatory infiltration or vessel wall necrosis) in 5/6 T patients (83%) and in 10/17 (59%) NT patients (p = 0,135). The infiltrate contained eosinophils in 2/6 T patients (33%) and in 4 out of 18 (22%) NT. The immunocytochemical characterization of inflammatory infiltrates showed predominantly CD45Ro positive reactive T-lymphocytes. Granuloma was not documented in any of our cases; also in literature, granuloma is rarely found in peripheral nerves. Perineurial microfasciculation was not seen in our cases. The authors looked for hemosiderin deposits in serial paraffin sections stained with HE of all nerve biopsies, but failed to find it. Semithin sections stained with toluidine blue revealed a variable loss of myelinated fibres. Signs of demyelination were not observed in teased fibres analysis. Electron microscopy confirmed that also non myelinated fibres were involved. Fibre loss was uniform in all studied fascicles in the T-group and in 10/17 (59%) in the NT-group, whereas it was focal in the remaining NT patients (p = 0,135). The degree of fibre loss was severe or moderate in 13/18 (72%) of NT patients and in 3/6 (50%) of the T-group, but the difference was not statistically significant (p = 0,742).

Treatment and follow-up

All the patients received the diagnosis of EGPA following the ACR criteria (4). Steroids were the mainstay of treatment in all patients. Cyclophosphamide was added to steroids in 4 NT and in 1 T patients. Azathioprine was never used during our time of follow-up. Length of follow-up ranged from 21 months (mean) in the T-group to 25 months in the NT-group (**table 3**). Clinical and neurophysiological follow-up were both available for all T patients, whereas in the NT group, clinical follow up was available for all patients, but neurophysiological for only 9/18 (50%). The neurological picture improved in all T patients (6/6 = 100%) while among NT patients it improved in 16/18 (89%), remained stable in 1/18 (5.5%) and worsened in 1/18 (5.5%). However, three NT patients died between 6 and 24 months after the onset of neuropathy. Death was caused by adult respiratory distress syndrome in two of them and by complications following surgery of upper respiratory tract in the third patient. Blood eosinophilia returned within normal limits in 23/24 patients.
For those NT patients for whom neurophysiological follow up was available, nerve conduction studies disclosed a stable pattern of MM in 3/9 (33%), an improvement in 3/9 (33%) and a worsening in the remaining 3/9 (33%). Likewise, in the T group 3/6 (50%) patients improved, 2/6 (33%) remained stable and 1/6 (17%) worsened (table 3).

Discussion

The pathogenesis of eosinophilic granulomatosis with polyangiitis is still debated. Although a major role has been attributed to withdraw of oral and inhaled steroids (23,29), which is reported in 88% of asthmatic patients who develop EGPA, this cannot be considered the only triggering factor, as the syndrome has been described also in non-asthmatic patients (2,3), in asthmatic patients not taking steroids (16,19) and after the administration of several medications such as macrolides (24), oestrogens (25), carbamazepine (26) and, more recently, LTAs drugs (11,12,13,14,15,16,17,18,19).
LTAs interfere with the synthesis of LTA4 from arachidonic acid by blocking 5 lipoxygenase activating protein (zafirlukast) while montelukast and pranlukast are antagonists of LTC4 and LTE4 (27). These medications have been used since 1998 to treat moderate or mild persistent asthma. The advantage in their use is the steroid sparing effect, and therefore the possibility to reduce steroid related side effects. The association between administration of LTAs and peripheral nerve involvement in patients affected by asthma, leading to florid eosinophilic granulomatosis with polyangiitis, has been reported since the release of these drugs on the market. In most of the previously described cases, however, the neuropathy appeared after steroid withdrawal, raising therefore some doubts about the role of LTAs in triggering EGPA related neuropathy (25). Just recently, an analysis of the FDA Adverse Event Reporting System seem to confirm that in most confirmed cases of EGPA, LTAs treatment is a suspect medication for triggering this syndrome (30). In the present study, among 24 patients with neuropathy and definite diagnosis of EGPA, we identified 6 cases that had previously been treated with montelukast, a leukotriene antagonist. To clarify the issue of LTAs as causative agent of EGPA neuropathy, we compared clinical, neurophysiological and peripheral nerve pathological features between the two groups, that only differed for exposure to montelukast. Unlike reported in most

small series of literature, in none of our patients previously treated with montelukast, steroid therapy was stopped before the onset of EGPA-related neuropathy, making therefore steroid withdrawal very unlikely as a causative factor. Demographic features, as well as asthma duration and systemic involvement, were remarkably similar, with the only exception of a relatively (although nonsignificantly) larger involvement of the nasal mucosa and higher systemic involvement in T patients. Presence of pANCA did not differ in the two groups. Neither clinical nor neurophysiological features seem to differ between T and non-T group: the overwhelming majority of patients presented with an axonal mononeuropathy multiplex. Axonal involvement was confirmed by sural biopsy, which revealed in all cases a variable degree of fiber loss. Signs of demyelination were not observed in teased fibers analysis. Epineurial vessel wall infiltrates of inflammatory cell (including eosinophil cells) were observed in 83% of T-cases and in 59% of NT-patients. In the T group, neuropathy onset was always preceded by systemic symptoms and the pattern of peripheral nerve involvement was a mononeuropathy multiplex. Unlike previous reports on LTAs-related neuropathy, our study was able to assess the course of the disease. Compared with non-treated patients, T-group showed a trend for a better outcome (but non-significant), as the clinical evolution was clinically more favorable in the latter (100% vs. 89% improvement) in parallel with the improvement of neurophysiologic parameters, which occurred in 50% of T but in only 33% of NT-patients despite similar treatment.

In summary, the analysis of our series suggests the following conclusions: 1) neuropathy related to EGPA does not seem to be related to steroid withdraw; this is true both in patients treated with LTAs, but also in the majority of those who had never been exposed to these medications; 2) the temporal co-relation with the administration of LTAs suggests as most obvious the interpretation of an "adverse drug reaction"; 3) no major differences between the two groups with the only exception of a relatively (although non significantly) larger involvement of nasal mucosa and a higher systemic involvement in the treated patients; 4) one or more as yet undisclosed trigger factors different from LTAs exposure or steroid withdraw might underlie the appearance of EGPA.

Strengths of the study are the consecutive recruitment of the studied cohort, the rigorous clinical and histological assessment and the ability to follow up patients. Some limitations derive from the small sample size and the inclusion criteria, which may not entirely rule out a selection bias.

Figure 1 *- Pathological features in nerve biopsies.*
A-C: Asymmetric fiber loss and axonal degenerations in nerve biopsy of case 5 (NT-group) (A) and mild fiber loss in case 19 (T-group) (C). (semithin sections, Toluidine blue).
B: Eosinophils infiltration in the wall of an epineurial vessel in case 6 (NT-group) (paraffin section, HE stain).
D: Perivascular inflammatory cell infiltration and necrosis of vesel wall in case 19 (paraffin section, HE stain)

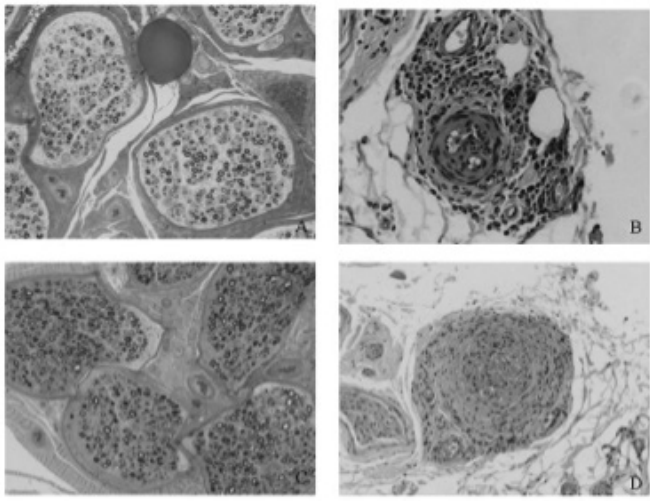

Table 1 *- General features of the patients studied.*

				ARA diagnostic criteria for CSS										
Case	**Age (years)/ sex**	**Asthma duration (years)**	**Blood eosinophils (%) at onset of symptoms**	**Paranasal sinus involvement**	**Chest involvement**	**PNS involvement**	**Tissue eosinophils**	**Other organs involvement**	**Other tissues biopsies performed & results**	**pANCA**	**Treatment for asthma before neuropathy onset**	**Steroid withdraw**	**Latency between NP onset & treatment with montelukast (days)**
1	48/F	7	53	-	-	MM	-	CNS hypereosin sy	-	na	CS βago	-	-
2	69/ M°†	<0,2	27	-	-	MM	-	muscle	-	+	CS	-	-
3	61/M	11	22	+	-	MM	-	muscle	-	na	CS βago	-	-
4	64/M†	4	6	+	+	MM	-	myelodisplastic sy	-	na	CS	-	-
5	52/M	16	20	+	na	MM	+	skin joints	-	-	CS	-	-
6	66/M	0,5	15	-	na	MM	-	aortic aneurism	-	-	βago	-	-
7	76/M	0,5	20	-	+	MM	-	skin	skin: N	-	none	-	-
8	60/F	10	50	+	+	MM	-	mucosal	skin: N	-	CS	-	-
9	46/F†	34	40	-	+	MM	+	-	-	+	CS	-	-
10	56/F	17	52	-	+	MM	+	muscle	BAL&BS: +	-	CS βago	-	-
11	62/F	4	23	-	+	PN	+	-	-	+	CS βago	-	-
12	31/F	0,6	27	-	-	PN	-	skin muscle	skin: N muscle:+	-	CS βago	-	-
13	55/F	1	65	+	-	MM	+	bowel renal	nasal polipus	+	CS βago	+	-
14	29/F	3	42	-	+	MM	+	skin	skin: + BAL&BS:+	+	CS βago	-	-
15	67/F	11	54	+	-	MM	+	-	BS:+	+	CS βago	-	-
16	69/M	6	63	+	-	MM	-	-	-	-	CS βago	+	-
17	62/F	19	33	-	-	MM	-	pericardium	-	-	CS βago	-	-
18	72/F	19	36	-	-	PN	-	-	-	-	CS	-	-
19	66/F	6	35	-	+	MM	+	-	BS:+	-	CS + M	-	2
20	49/F	7	35	+	-	MM	+	small joints	-	-	CS + M	-	48
21	46/M	6,5	28,9	+	+	MM	-	-	-	+	CS + M	-	1-3
22	59/F	19	59	+	+	MM	-	-	BAL:+	+	CS + M	-	1
23	51/M	1,5	33	+	+	MM	+	-	BS:+	+	CS + M	-	1
24	56/M	10	58	+	-	MM	-	-	skin:-	-	βago + M	-	150

F = female; M = male; PN = polyneuropathy; † = dead; MM = mononeuropathy multiplex; + = present; - = absent; na = not available; N = normal; hypereosin sy = hypereosinophilic syndrome; CNS = central nervous system; BS = bronchoscopy; BAL = bronchoalveolar lavage; + = abnormal; CS = corticosteroids; βago = βagonist; M = montelukast; ANCA = antinuclear cytoplasmic antibodies; sy = syndrome.

Table 2 *- Statistic analysis of demographic, clinical and laboratory features.*

Variable	Non Treated group	Treated group	P value
Number of patients	18	6	
Age (years)	58 ± 13 (mean +/-SD)	54.5 ± 7 (mean +/-SD)	0.533
Sex (M/F)/%	39/61	50/50	0.665
Asthma duration (years)	9.14 ± 9 (mean +/- SD)	8.33 ± 6 (mean +/-SD)	0.805
Blood eosinophil count (%) at onset of PNS involvement	36 ± 17	41 ± 13	0.488
Nasal polyposis	7/18 (39%)	5/6 (83%)	0.077
Chest involvement	4/6 (66%)	7/16 (44%)	0.635
Tissue eosinophilia	7/18 (39%)	3/6 (50%)	0.665
pANCA	6/15 (40%)	3/6 (50%)	0.523
Mean clinical follow-up (month)	25 (mean)	21 (mean)	0.628

Table 3 *- Summary of symptoms at onset, electrophysiological findings and outcome at follow up.*

Case	General symptoms before onset of neuropathy	Neurological symptoms at onset of neuropathy and limb affected	Neurophysiological findings at onset of symptoms	Clinical outcome or cause of death (follow up in months)	Neurophysiological follow-up
1	none	motor LL	MM sm LL axonal	+ sm (6)	=
2	arthromyalgia dyspnoea rhinorrea	sm UL	MM m>s UL>LL axonal	ARDS (6)	PNsm,axonal
3	arthromyalgia fever	sm ULLL	MM m>s ULLL Axonal	+ s>m (36)	-
4	fever	sm ULLL	MM sm ULLL axonal	ARDS (2)	Na
5	none	sm LL	MM m>s LL axonal	+ sm (36)	Na
6	none	sm LL, symmetric	MM m>s LL axonal	+ sm (24)	Na
7	acute dyspnoea livedo reticularis	motor LL	MM m>s U&L axonal	+ sm (36)	+

Case	General symptoms before onset of neuropathy	Neurological symptoms at onset of neuropathy and limb affected	Neurophysiological findings at onset of symptoms	Clinical outcome or cause of death (follow up in months)	Neurophysiological follow-up
8	none	s LL	MM sm ULLL axonal	+ (3)	Na
9	arthromyalgia	s LL	MM s>m LL axonal	+ sm (21)	=
10	arthromyalgia	sm LL	MM sm LL>UL axonal	- (2)	PNsm, axonal
11	fever	sm LL, symmetric	PN sm LL axonal	+ (90)	+
12	livedo, abdominal pain myalgia	s LL, symmetric	PN s, LL axonal	Na	Na
13	arthromyalgia	sm LL	MM m>s LL axonal	+ sm (60)	Na
14	fever, weight loss cramps	sm LL	MM sm LL axonal	+ (34)	+
15	fever	sm UL	MM m>s ULLL axonal	+ sm (59)	Na
16	none	s>m UL	MM sm ULLL axonal	+ sm (2)	=
17	none	sm ULLL	MM sm UULL axonal	+ sm (3)	Na
18	arthromyalgia	s ULLL	PN sm LL>UL axonal	=sm (3)	Na
19	fever, dyspnoea	sm LL	MN sm LL>UL axonal	+ sm (36)	+
20	weight loss, fever arthralgia	sm LL	MM m>s LL axonal	+s>m (25)	-s; +m
21	skin lesions	sm ULLL	MM sm ULLL axonal	+ sm (21)	=
22	headache	sm ULLL	MM s>m UL>LL axonal	+ sm (8) coma for SAH	+
23	none	s LL	MM s>m LL axonal	+sm	+
24	fever cough	sm ULLL	MM m>s UL>LL Axonal	+ m (15)	=

LL = lower limbs; UL = upper limbs; ULLL = four limbs; PN = polyneuropathy; MM = moneuropathy multiplex; s = sensory; m = motor; na = not available; ARDS = acute respiratory dystress syndrome; + = improvement; - = worsening; = = unchanged; SAH = subarachnoid haemorrhage

Table 4 *- Findings of nerve biopsy.*

Case	Degree of myelinated fibre loss	Pattern of fibre loss	Axonal degeneration	Epineurial infiltrates	Eosinophils infiltrate	Necrotizing vasculitis
1	severe	uniform	++ / -	-	-	-
2	mild	uniform	+++ / -	+	-	-
3	severe	uniform	+++ / -	-	-	-
4	very mild	focal +	++ / -	-	-	-
5	moderate	uniform	+++ / -	++	+	+
6	mild	uniform	+ / +	-	-	-
7	moderate	focal ++	+ / +	+	-	-
8	mild	uniform	++ / -	+	-	-
9	severe	focal +	++ / +	+++	+++	+
10	severe	uniform	+++ / -	-	-	-
11	severe	uniform	+++ / -	+++	-	+
12	mild	uniform	+	-	-	-
13	severe	uniform	no fibres	++	+	+
14	severe	uniform	+++ / -	+	-	-
15	mild	focal +	+ / +	+	+	+
16	severe	focal +	+++ / +	-	-	-
17	moderate	focal ++	++ / +	-	-	-
18	moderate/severe	focal +	++ / -	+	-	-
19	mild	uniform	+ / +	++	+	+
20	mild	uniform	++ / -	++	-	-
21	severe	uniform	+++ / +	+++	+	-
22	moderate	uniform	+++/-	+	-	-
23	mild	uniform	uniform	+	-	-
24	severe	uniform	+++/-	++	-	-

+/- = very mild; + = mild; ++ = moderate; +++ = severe; - = absent

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