

## Malignant mental nerve neuropathy: Systematic review

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### Abstract

**Abstract:** Malignant mental neuropathy (MMN) is a neurological manifestation of cancer, characterized by the presence of hypoesthesia or anesthesia restricted to the territory of the mental branch of the mandibular nerve. A systematic review of the literature has been made on MMN, analyzing the etiology, pathogeny, clinical characteristics, complementary tests and the prognosis. Sixteen studies, providing 136 cases were selected. Breast cancer and lymphomas were the most frequently associated malignant diseases. The most frequent pathogenic mechanisms producing neurological involvement were: peripherally, mandibular lesions; and centrally, tumors at the base of the cranium. Regarding clinical characteristics, manifestation of MMN was the primary symptom of malignant disease in 27.7% of cases, and a first symptom of recurrence in 37.7%. The group of selected studies included 50 orthopantomographs, 9 mandibular computed tomographies and 50 radiographic examinations of the cranial region. The most affected region was the mandible. The appearance of MMN is an ominous prognosis for the progression of the disease, with a mortality of 78.5% within a mean of 6.9 months.

**Key words:** Numb chin syndrome, mental nerve neuropathy, mental numbness.

### Introduction

Malignant mental neuropathy (MMN) is a neurological manifestation of cancer, characterized by numbness in the region innervated by the mental nerve: skin of the chin, oral mucosa and lower lip of the affected hemisphere (1).

According to Massey et al. (2) in 47% of cases it is the first clinical manifestation of malignant disease or its recurrence. Its appearance is associated with an ominous prognosis (3). Numb chin often goes unnoticed, and may indicate tumor metastasis (1). The first article on MMN was published in 1963 by Calverley and Mohnac (4) who presented three patients and introduced the term 'numb chin syndrome'. The literature on MMN is wide in clinical

series with few patients and descriptions of isolated cases; the study with most patients published to date was made in 2002 by Lossos and Siegal (3) with 42 cases.

The aim of this systematic review on MMN is to study the etiology, the pathogeny, the clinical characteristics, complementary tests and prognosis.

### Search strategy and inclusion criteria

A search in PubMed was made of all studies published on MMN to November 2007. The following key words were used: 'numb chin syndrome' for which 51 references were found, 'mental nerve neuropathy' with 198, and 'mental numbness' with 148. Inclusion criteria were articles published on MMN with three or more patients and a minimum

follow-up of one year, providing sixteen studies with a total of 136 cases (1-16).

### Etiology

MMN is associated with different types of cancer. Of the 136 cases analyzed, the most frequent primary malignant disease was breast cancer in 40.4% of cases, followed by lymphomas in 20.5%, prostate cancer in 6.6% and leukemia in 5.1%. The remainder of the cases were constituted by a miscellany of lesions (Table 1).

### Pathogeny

The mechanisms by which MMN is produced are not well known, and different hypotheses have been proposed. The origin may be peripheral or central (6). Peripherally, mandibular bone tumors, with direct nerve infiltration, were the most frequent original neoplasm, being found in 50% of cases (3,13,15). Centrally, the most frequent were tumors located at the base of the skull; these lesions may cause bone destruction or infiltration of the leptomeninges, close to the gasserian ganglion region (3). For Lossos and Siegal (3) MMN is produced by bone lesions at the base of the skull in 14% of cases, and in 22% by isolated leptomeningeal seeding. Other authors also find leptomeningeal involvement: Horton et al. (8) contributed 13 patients with breast cancer and MMN, 5 of whom died, leptomeningeal carcinomatosis was found in the autopsy of all these cases. Rubinstein (7) presented 4 patients with non-Hodgkin's lymphoma and MMN, finding invasion of the meninges and the cranial nerve branches in the post-mortem examination.

Occasionally, no relationship between MMN and a distant neoplasia can be determined (1). According to Pascual et al. (9) there is no single pathogeny that can explain all cases. For Lossos and Siegal (3), the cause was unknown in 11% of patients. Massey et al. (2) found no determinant cause for MMN in a series of 19 patients.

### Clinical characteristics

MMN is characterized by numbness confined to the chin and lower lip, which is the consequence of loss of function of the terminal sensory division of the mandibular branch of the trigeminal nerve; as a result of this lack of sensitivity, lesions caused by biting of the lower lip can be found (1, 5).

The following characteristics were analyzed in the 16 selected articles (1-16): the age and sex of the patients, the location of the symptom (unilateral/bilateral), the frequency of associated pain, the percentage in which the appearance was the first sign of malignant disease and as the first sign of relapse (Table 2).

The weighted mean age of the patients was 47.8 years; there were 81 females and 55 males. The affected side was specified in 117 patients of the entire sample, being unilateral in 97, and bilateral in 20. Lossos and Siegal (3),

in 1992, found 10% with bilateral involvement, against 14.7% in the present review. Of the 20 patients with bilateral involvement, the primary malignant disease was determined in 16 (Table 2).

Pain is an infrequent symptom in MMN (1,2,8). Neurogenic pain was associated with MMN in 10 of the 136 patients. According to Calvin et al. (17), tumor compression of the sensory trigeminal roots causes demineralized areas which would be the cause of pain.

The appearance of MMN may be warning sign of a systemic cancer or of its recurrence (7). Massey et al. (2) detected MMN prior to the diagnosis of cancer in 47% of 19 patients. For Vadell et al., MMN was the first sign of neoplastic relapse in 100% of their patients (11). In the present review, MMN appears as the primary manifestation of disease in 27.7% of cases and is the first symptom of a tumor recurrence in 37.7%.

### Diagnosis and complementary tests

Against the appearance of mental neuropathy, the presence of a malignant or benign lesion should be investigated along the trigeminal nerve (11,12). A clinical examination is not sufficient to locate a lesion (16), therefore the appearance of a mental neuropathy obliges a complete radiographic examination of the trigeminal nerve (10). Mandibular lesions were found in 51 cases, cerebral in 16, consisting of meningeal carcinomatosis, the base of the skull was involved in 15 patients, and in 47 the location of the lesion could not be determined (Table 3).

In the articles studied, orthopantomographs were made in 50 of 130 cases, with positive findings in 17; 50 examinations of the cranial region were requested (cranial computed tomography, cranial radiography, or MRI of the brain) finding lesions in 30 cases. Out of 9 mandibular computed tomographies, lesions were found in 3 patients (Table 3).

### Prognosis

MMN in patients with neoplasia may indicate recurrence of the tumor, and is associated with an ominous prognosis. In the sixteen studies reviewed, a mortality of 78.5% (66 of 84 patients) was found, with a weighted mean survival of 6.9 months (Table 4).

**Table 1.** Etiology.

AUTHOR	N° cases	Breast cancer	NH Lymphoma	Prostate cancer	Leukemia	Myeloma/ Plasmocytoma	Lung cancer	Hodgkin's Disease	Sarcoma	Myeloma	Cavum	Melanoma	OU	Others
1963 Calverley and Mohnac <sup>4</sup>	5	3	-	1	-	-	-	1	-	-	-	-	-	-
1965 Rozman and Erill <sup>5</sup>	5	-	-	2	-	2	-	-	-	-	-	-	1	-
1969 Nobler <sup>6</sup>	8	-	5	-	-	1	-	1	-	1	-	-	-	-
1969 Rubinstein <sup>7</sup>	4	-	4	-	-	-	-	-	-	-	-	-	-	-
1973 Horton et al <sup>8</sup>	15	13	2	-	-	-	-	-	-	-	-	-	-	1
1981 Massey et al <sup>2</sup>	19	3	6	1	2	1	1	-	2	1	-	1	1	2
1985 Barret <sup>10</sup>	4	-	2	-	2	-	-	-	-	-	-	-	-	-
1986 Pascual et al <sup>9</sup>	3	2	-	-	-	-	-	-	-	-	1	-	-	-
1989 Vadel et al <sup>11</sup>	5	3	-	1	-	-	1	-	-	-	-	-	-	-
1990 Peñarocha et al <sup>12</sup>	3	-	-	1	-	-	1	-	-	-	-	-	-	-
1992 Burt RK et al <sup>13</sup>	4	-	-	1	-	-	-	2	-	-	1	1	-	1
1992 Lossos and Siegal <sup>3</sup>	42	27	6	-	-	-	-	-	2	-	-	-	-	7
1997 Hiraki et al <sup>14</sup>	3	-	-	-	3	-	-	-	-	-	-	-	-	-
1999 Ojanguren et al <sup>15</sup>	4	-	3	-	-	1	-	-	-	1	-	-	-	-
2000 Laurencet et al <sup>1</sup>	5	2	-	2	-	-	1	-	-	-	-	-	-	-
2006 Peñarocha et al <sup>16</sup>	7	2	-	-	-	-	-	-	-	-	-	-	-	-
<b>TOTAL</b>	136	55	28	9	7	5	4	4	4	3	2	2	2	11
<b>Percentages</b>		40.4%	20.5%	6.6%	5.1%	3.8%	2.9%	2.9%	2.9%	2.2%	1.4%	1.4%	1.4%	8%

N°: number

NH: non Hodgkin's

OU: origin unknown

**Table 2.** Clinical characteristics.

AUTHOR	Nº Cases	Mean age	Sex M/F	Involvement Unilateral/Bilateral	Etiology NMM bilateral	Mandibular pain	1 <sup>st</sup> sign of disease %	1 <sup>st</sup> sign of recurrence %
1963 Calverley and Mohnac <sup>4</sup>	5	42.4	2/3	5 / 0	-	1	20	20
1965 Rozman and Erill <sup>5</sup>	5	55.2	3/2	4 / 1	Prostate cancer	-	40	0
1969 Nobler <sup>6</sup>	8	49.5	7/1	6 / 2	lymphosarcoma	-	12.5	37.5
1969 Rubinstein <sup>7</sup>	4	38.5	1/3	2 / 2	Neuroblastoma /lymphoma	-	100	0
1973 Horton et al <sup>8</sup>	15	53.4	1/14	15 / 0	-	1	-	-
1981 Massey et al <sup>2</sup>	19	45.4	14/5	- / -	-	5	47.3	0
1985 Barret <sup>10</sup>	4	37	3/1	2 / 2	Non Hodgkin's	-	25	50
1986 Pascual et al <sup>9</sup>	3	60.6	1/2	1 / 2	Breast cancer	-	33.3	66.6
1989 Vadell et al <sup>11</sup>	5	47.4	3/2	4 / 1	Prostate cancer	-	0	100
1990 Peñarocha et al <sup>12</sup>	3	53	2/1	2 / 1	Prostate cancer	-	66.6	33.3
1992 Burt RK et al <sup>13</sup>	4	52.5	2/2	4 / 0	-	-	0	75
1992 Lossos and Siegal <sup>3</sup>	42	48	5/37	38 / 4	-	-	**8.3	**86.1
1997 Hiraki et al <sup>14</sup>	3	16.6	2/1	2 / 1	Leukemia	-	100	0
1999 Ojanguren et al <sup>15</sup>	4	48.5	3/1	3 / 1	Lymphoma	-	0	0
2000 Laurencet et al <sup>1</sup>	5	57	2/3	2 / 3	Lung cancer	-	20	40
2006 Peñarocha et al <sup>16</sup>	7	47	4/3	7 / 0	-	3	42.8	57.1
<b>TOTAL</b>	136	47.8 <sup>¥</sup>	55/81	97* / 20*	-	10	27.7	37.7

Nº: number

¥ : weighted mean age

M: male /F: female

\* On 117 patients

\*\* On 36 of the 42 patients, 6 were excluded for lack of follow-up

**Table 3.** Complementary tests.

AUTHOR	N° Patients	Location				Orthopantomography			CT mandibular			CT or cranial X-ray / MRI cerebral		
		C	BC	M	U	Total	+	-	Total	+	-	Total	+	-
1963 Calverley and Mohnac <sup>4</sup>	5	-	-	3	2	5	1	4	-	-	-	1	1	0
1965 Rozman and Erill <sup>5</sup>	5	-	-	3	2	3	2	1	-	-	-	5	3	2
1969 Nobler <sup>6</sup>	8	-	-	3	5	-	-	-	-	-	-	1	1	0
1969 Rubinstein <sup>7</sup>	4	4	-	-	-	-	-	-	-	-	-	4	1	3
1973 Horton et al <sup>8</sup>	15	1	4	2	8	8	2	6	-	-	-	15	8	7
1981 Massey et al <sup>2</sup>	19	-	-	5	14	12	4	8	-	-	-	2	0	2
1985 Barret <sup>10</sup>	4	-	-	-	4	1	1	0	-	-	-	-	-	-
1986 Pascual et al <sup>9</sup>	3	-	1	1	1	3	1	2	-	-	-	1	1	0
1989 Vadell et al <sup>11</sup>	5	-	-	4	1	5	0	5	-	-	-	3	1	2
1990 Peñarrocha et al <sup>12</sup>	3	-	1	1	1	3	0	3	-	-	-	2	1	1
1992 Burt RK et al <sup>13</sup>	4	-	-	1	3	-	-	-	-	-	-	4	2	2
1992 Lossos and Siegal <sup>3</sup>	36*	8	5	18	4	-	-	-	-	-	-	-	-	-
1997 Hiraki et al <sup>14</sup>	3	-	-	3	-	3	3	0	-	-	-	-	-	-
1999 Ojanguren et al <sup>15</sup>	4	-	-	4	-	-	-	-	-	-	-	4	4	0
2000 Laurecet et al <sup>1</sup>	5	1	3	-	1	-	-	-	3	0	3	4	4	0
2006 Peñarrocha et al <sup>16</sup>	7	2	1	3	1	7	3	4	6	3	3	4	3	1
<b>TOTAL</b>	<b>130</b>	<b>16</b>	<b>15</b>	<b>51</b>	<b>47</b>	<b>50</b>	<b>17</b>	<b>33</b>	<b>9</b>	<b>3</b>	<b>6</b>	<b>50</b>	<b>30</b>	<b>20</b>

N°: number

\*of the 42 patients, 6 were excluded for lack of follow-up

C: Cerebral. BC: Base of cranium M: Mandibular. U: Unknown

+ or -: lesion detected or lesion not detected

**Table 4.** Prognosis.

AUTHOR	N° Patients	Mortality	Weighted mean in months
1963 Calverley and Mohnac <sup>4</sup>	5	4	13
1965 Rozman and Erill <sup>5</sup>	5	1	2
1969 Nobler <sup>6</sup>	8	6	4
1969 Rubinstein <sup>7</sup>	4	4	16
1973 Horton et al <sup>8</sup>	15	13	5
1981 Massey et al <sup>2</sup>	19	16	5
1985 Barret <sup>10</sup>	4	3	2
1986 Pascual et al <sup>9</sup>	3	3	6
1989 Vadell et al <sup>11</sup>	5	2	22
1990 Peñarrocha et al <sup>12</sup>	3	2	2
1992 Burt RK et al <sup>13</sup>	4	-	-
1992 Lossos and Siegal <sup>3</sup>	36*	-	8
1997 Hiraki et al <sup>14</sup>	3	0	0
1999 Ojanguren et al <sup>15</sup>	4	4	5
2000 Laurecet et al <sup>1</sup>	5	3	10
2006 Peñarrocha et al <sup>16</sup>	6**	5	9.8
<b>TOTAL</b>	<b>129</b>	<b>66 of the patients</b>	<b>6.9<sup>¥</sup></b>

\* of the 42 patients, 6 were excluded for lack of follow-up

\*\* of the 7 patients one was lost to follow-up after 8 months

¥ weighted mean in months

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