Ital J Neurol Sci (1998) 19:133-149

REVIEW

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Meningeal metastases: clinical aspects and diagnosis

Received: 20 October 1997 / Accepted: 24 March 1998

Abstract The authors review the clinical and diagnostic aspects involved in leptomeningeal disease due to solid tumours, leukaemias and lymphomas. The importance of the combination of clinical findings with cerebral spinal fluid (CSF) examination and imaging studies in making an early diagnosis is underlined. The raising prevalence of this complication of systemic cancer deserves specific attention on the part of neurologists involved in consultation liason with general medicine and oncology.

Key words Leptomeningeal disease · Leptomeningeal metastases · Diagnosis · Meningeal carcinomatosis · Cancer complications.

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Introduction

Leptomeningeal disease (LMD) or leptomeningeal metastases is the term which is now preferred to describe both solid tumours seeding the leptomeninges (meningeal carcinomatosis) and meningeal leukaemia or lymphoma. Other terms such as carcinomatous meningitis are less correct, implying an inflammatory process which may or not be associated with LMD [1].

LMD is a severe and relatively common neurologic complication of systemic neoplasms. An early diagnosis is very important to improve the chances of effective treatment. LMD should be suspected from clinical signs and symptoms, and established by appropriate laboratory examinations. However, the clinical manifestations of this illness may be quite obscure and the diagnosis antemortem is at times difficult.

Epidemiology

First described in 1870 [2], leptomeningeal carcinomatosis ("meningitis carcinomatosa") [1] was thought to be a rare disorder, often diagnosed only after death (Table 1) [3-6]. Only in last three decades is leptomeningeal seeding increasingly being recognised as a cause of neurologic disability in life. The rise in prevalence of LMD is apparent and may be due to increased clinical awareness and to improved diagnostic techniques [1]. For example, the recognition of leptomeningeal carcinomatosis during the lifetime of patients affected by small cell lung cancer changed from 39% of the affected cases prior to 1977 to 88% in 1982 [7]. There is also evidence that the incidence of metastases to the leptomeninges is increasing, in association with better therapies for systemic malignancies and consequent prolonged survival times due to control of systemic diseases. Micro-metastases to the central nervous system (CNS)

Table 1 Autoptic incidence of leptomeningeal metastases in patients with cancer

Reference	Period	Autopsies *n*	Leptomeningeal tumours *n (%)*	Leptomeningeal tumours without other intracranial masses *n (%)*	Leptomeningeal tumours without metastases in other regions *n (%)*
Posner Chernick [4]	1970-1976	2374	184 (8)	63 (3)	-
Gonzales-Vitale, Garcia-Bunnel [5]	Before 1976	2227	-	18 (0.8)	7 (0.3)[a]
Takakura et al. [6]	1950-1970	3359	118 (3.5)	-	-

[a] 40 with meningeal carcinomotosis

could already be present and asymptomatic when systemic chemotherapy is administered and may be protected from chemotherapy agents by the blood-brain barrier. Patients not dying early from tumour dissemination to other organs will then develop CNS disease, and LMD in particular, due to the growth of this "sanctuary" cell population. An increased frequency of leptomeningeal metastases has been observed with oat cell carcinoma [7, 8], some histologic subtypes of lymphomas [9-11], breast carcinomas [12-14] and perhaps ovarian carcinoma and sarcomas [1, 15]. Also, as a consequence of more effective chemotherapy, the frequency of the systemic disorder leptomeningeal leukaemia increased, until specific prophylactic treatment of the central nervous system was instituted [16-18].

Leptomeningeal tumoral seeding is frequently seen in modern autoptic studies of cancer patients [4-6]. Generally, the likelihood of leptomeningeal seeding is higher with wider systemic spread of the tumour. Usually LMD occurs as a late complication of tumoral illness [7], however it sometimes represents the first clinical evidence of cancer [5] (Table 2) [5, 19, 20] and it should be in the differential diagnosis of every patient with chronic progressive neurological disturbances. LMD is usually a late event in breast cancer and leukaemia, with neurological symptoms occurring years after the diagnosis of the primary neoplasms [21, 22] when most patients already have metastases to lung, liver and bone (Table 2) [19, 20, 23]. In breast cancer, it is becoming more frequent to find LMD as a further relapse in patients with metastatic disease to other organs (e.g. lung or bone) which initially responded to treatment [14]. In many patients, other CNS metastases such as brain or epidural lesions [19], are found concurrently with LMD. The time lag between diagnosis of the primary malignancy to the leptomeningeal spread differs from a few days to more than ten years, ranging most often between 6 months and 3 years [19].

In adults, breast and lung cancer, lymphomas, leukaemia and malignant melanoma are the most frequent tumours that spread to leptomeninges [11, 19, 20, 23, 24], while in children LMD is usually due to leukaemia (Table 3) [4, 5, 17, 19, 20, 25-28]. Adenocarcinomas more commonly infiltrate leptomeninges than do sarcomas, epidermoid carcinomas and lymphoma [23, 29]. LMD may also rarely develop from primary neoplasms confined to meninges, as in lymphomas [30], melanomas [31, 32] and rhabdomyosarcomas [33].

Breast cancer is the most frequent cause of LMD accounting for about 30% of cases [13, 19, 20, 29].

Table 2 Metastases other than leptomeningeal at time of presentation

Reference	Patients examined *n*	Evidence of systemic metastases *(%)*	Leptomeningeal carcinomatosis as the presenting complaint *(%)*
Wasserstrom et al. [19]	90[a]	64[b]	6
Kaplan et al. [20]	63	72[c]	10[d]

[a] Only solid tumours.
[b] 34% of patients showed other central nervous system or epidural metastatic signs
[c] 90% solid tumour, 60% lymphoma; 47% leukemia
[d] 3% solid tumour, 13% lymphoma, 18% leukemia

Table 3 Primary tumours in leptomeningeal metastases

Tumour	Primary tumours, *n (%)*					
	Gonzales Vitale, Garcia-Bunnel [5] (*n*=18)	Posner, Chernik [4] (*n*=68)	Wasserstrom et al. [19] (*n*=90)	Sause et al. [27] (*n*= 26)	Kaplan et al. [20] (*n*=63)	Chamberlan et al. [28] (*n*=61)
Breast	4 (22)	11 (16)	46 (51)	17 (65)	17 (27)	9 (15)
Lung	7 (39)	4 (6)	23 (26)	4 (15)	14 (22)	9 (15)
- Adenocarcinoma	5 (28)	-	13 (14)	-	7 (11)	-
- Epidermoid	-	-	3 (3)	-	2 (3)	-
- Oat cell carcinoma	1 (6)	-	6 (7)	-	5 (8)	-
- Anaplastic large cell	1 (6)	-	1 (1)	-	-	-
Melanoma	-	6 (9)	11 (12)	3 (12)	-	4 (7)
Gastrointestinal	4 (22)	3 (4)	1 (1)	-	-	2 (3)
Genitourinary	2 (11)	-	5 (6)	2 (8)	-	3 (5)
Head and neck	-	-	2 (2)	-	-	11 (18)
Lymphoma	-	15 (22)	-	-	15 (24)	17 (28)
- Non Hodgkin's	-	13 (19)	-	-	13 (21)	-
- Hodgkin's	-	2 (3)	-	-	1 (2)	-
- Burkitt's	-	-	-	-	1 (2)	-
Leukaemia	-	28 (41)	-	-	17 (27)	6 (10)
- Acute myelogenous	-	5 (7)	-	-	9 (14)	-
- Acute lymphocytic	-	21 (31)	-	-	5 (8)	-
- Chronic lymphocytic	-	-	-	-	2 (3)	-
- Chronic myelogenous	-	-	-	-	1 (1)	-
Undetermined	1 (6)	-	-	-	-	-
- Adenocarcinoma	1 (6)	-	2 (2)	-	-	-
- Sarcoma	-	1 (1)	-	-	-	-

n (%)

Consequently, LMD is slightly more frequent in women [19, 20]. In a comparative study, brain metastases from infiltrating lobular breast carcinoma were only two times more frequent than leptomeningeal metastases [34].

Carcinoma of the lung is the primitive neoplasm in about 20% of cases of LMD [7, 19, 20, 29, 35]. The majority of these patients have an adenocarcinoma or an oat cell carcinoma; rarer are epidermoid tumours and poorly differentiated large cell carcinoma [19, 20]. In small cell lung cancer, LMD is a frequent complication, particularly in non-responders to chemotherapy. Its prevalence increases with time since diagnosis [4, 7, 36].

Malignant melanoma ranks third as the primary tumour in LMD, excluding lymphomas and leukaemia [4, 19, 29, 37]. Melanoma may also originate directly from the meninges and be confined to them [31, 32, 38].

Genitourinary tumours [19] of the prostate [39] and bladder [40, 41], gynaecological tumours such as squamous cell carcinoma of cervix and ovarian carcinoma [42-44], head or neck malignancies [19, 45, 46], and gastric [1, 25] and rectal [47] carcinoma can all occasionally cause LMD. Cases of meningeal carcinomatosis by carcinoid [48, 49], Ewing's sarcoma [15] and rhabdomyosarcoma [50] have also recently been reported.

LMD frequently originates from non-Hodgkin's lymphomas [4, 11, 20, 51-54] and rarely from Hodgkin's lymphoma [4, 20, 55]. The prevalence of LMD in lymphomas is increasing in the young, since it is associated to AIDS-related lymphoma [54]. In adults affected by non-Hodgkin's lymphoma, LMD is more frequent in patients with bone marrow invasion [11, 51]. Meningeal lymphoma is more often metastatic [56] but in some cases it develops from direct diffusion from parenchymal neoplasms; primary meningeal lymphomas have also been observed [30].

LMD is often due to acute lymphocytic leukaemia and acute myelogenous leukaemia cells [4, 20, 57]. Less frequently it develops from dissemination of chronic lymphocytic leukaemia [20, 58]. Also, mycosis fungoides and multiple myeloma can involve the leptomeninges [59-61]. Leukaemia is frequently complicated by leptomeningeal involvement in both adults and children [4, 18, 20, 62].

Primary nervous system tumours may diffuse to the leptomeninges. This is typical in children affected by medulloblastoma [63, 64]. Sometimes the primitive tumour cannot be clearly identified, especially when it is an adenocarcinoma [19].

Clinical findings

LMD usually presents with neurologic signs and symptoms at more than one level of the neuraxis, including the brain, cranial nerves and spinal roots [20, 23]. A careful clinical history and neurological exam will disclose in most cases multilevel involvement of the nervous system. Neurological signs can, however, be confined only to the brain, cranial nerves or spinal region at first presentation and progress only later [19]. Nuchal rigidity, or neck or back pain arising from irritation of the leptomeninges can be the dominating clinical finding [20].

The onset of neurological illness in patients with known cancer should raise the suspicion of LMD. In cases of solid tumour metastases, it is rare to find LMD not associated with systemic metastases. On the contrary, in lymphomas and leukaemias LMD is often found without evidence of systemic disease [1, 20]. No other clinically significant difference can be found in association with any specific tumour type [19, 20].

LMD typically has an insidious onset with a chronic course, and neurological deficits are found early in the course of the illness. Differential diagnosis with infectious meningitis is based on the acute course, with the presence of fever preceding neurological deficits [1].

LMD can cause neurological symptoms and signs in several ways. The seeding of tumour cells along the CSF absorption routes may produce increased intracranial pressure and hydrocephalus in a significant percentage of patients. Cognitive deficits and headache are better explained by this mechanism. Brain, spinal cord and nerve root symptoms, such as partial seizures, motor and sensory deficits and psychiatric disturbances, may occur from direct compression or invasion of these structures. Tumour cell cuffs along arteries in Virchow-Robins spaces may provoke ischaemic-type symptoms, such as transient ischaemic attacks. Finally, the competition for glucose and other nutritive elements between growing tumours and the nervous system may account for some of the disturbances in LMD.

Symptoms and signs

Neck or back pain which is focal or radiating to the limbs is probably the most common initial symptom, representing 58% of cases in one series [20]. Back pain alone in patients with known cancer is an often overlooked initial symptom of LMD.

About half of patients initially complain of cerebral symptoms (Table 4) [10, 11, 19-21, 23, 28, 29, 35, 65, 66]. Headache is one of the most frequent symptoms but pain in the neck or back or pain of radicular type is the single most common initial complaint [19, 20, 23, 29, 51, 67]. Headache is frequently the presenting symptom of meningeal carcinomatosis, and its prevalence only slightly increases during the course of the illness [23]. Headache is bifrontal in some patients, while in others it is either diffused or located at the base of the skull, radiating into the neck. Headache is often associated with nausea and vomiting or light-headedness [19]. Rarely, it may mimic migraine or cluster headaches [1, 68]. It may be associated with increased intracranial pressure, in which case typical headaches may occur in waves due to increased intracranial pressure episodes [1]. Change in mental status is the second most frequent complaint with lethargy, delirium or only memory impairment [20, 69]. During the course of illness, mental alterations occur in the majority of patients [20, 23, 29]. In a few patients anxiety disorders and psychotic behaviour including paranoid ideation delusions and hallucinations have been described [69]. Rarely, meningeal carcinomatosis presents itself at first with loss of consciousness without seizures, probably related to increased intracranial pressure [1, 19]. Seizures, both generalised and focal, may be the presenting complaint [19, 20, 23, 29]. Non-convulsive status epilepticus, mistaken for delirium, has been reported [70, 71]. Less specific symptoms such as persistent nausea and vomiting, dizziness and light-headedness, and difficulties in speech can be found [1, 19, 35]. Diabetes insipidus can complicate LMD, more often in breast carcinoma [19, 72]. Diabetes insipidus occurs in 1% of patients with breast cancer [72]. Metastatic lesion of the posterior pituitary is associated with diabetes insipidus in 20% of cases [73]. Less commonly, leptomeningeal neoplasms cause diabetes insipidus involving the pituitary stalk in its passage through the subarachnoid space [74, 75].

The most frequent sign (Table 5) [10, 11, 19-21, 23, 28, 29, 35] revealed by a neurological examination of brain functions is cognitive impairment [19, 20, 23, 29, 65, 66], frequently associated with a reduction of vigilance [20]. Wide-based, ataxic gait is frequently described [19, 20]; rarer are papilloedema and hemiparesis [19]. Two reports described a rare syndrome, the encephalitic form of metastatic carcinoma, caused by leptomeningeal neoplasm invading the adjacent brain parenchyma, and characterised by cognitive disorders, frequent seizures and focal brain deficits [76, 77]. Neuroradiological exams in this syndrome are negative, due to the microscopic character of the alterations [78]. Hyponatraemia secondary to cerebral salt wasting was described in a patients suffering from meningeal metastasis due to lung cancer [79]. In another patient, central hyperventilation was observed [80].

Cranial nerve symptoms (Table 6) [19-21, 23, 29, 35, 65, 66] are an initial complaint in a third of patients [19, 23, 67] and they intervene during the course of illness in two-thirds of this population [11, 20, 29]. The commonest symptom is dyplopia [19, 23]. Hearing loss is the second most frequent symptom [19, 23]; it may start suddenly [81], but usually develops within several weeks. Other frequent complaints are facial numbness and visual loss [19]. Sometimes visual loss is the first symptom [19]; it is a frequent disturbance in

Table 4 Cerebral symptoms in leptomeningeal carcinomatosis at the time of diagnosis

Reference	Cases with cerebral symptoms, *n* (%)							
	Headache	Nausea or vomiting	Mental change	Loss of consciousness	Seizures	Dizziness and light headedness	Aphasia dysarthria	Diabetes insipidus
Olson et al. [23] (*n*= 50)	19 (35)	-	12 (24)	-	4 (8)	-	-	-
Little et al. [29] (*n*= 29)	17 (58)	-	14 (48)	-	4 (14)	-	-	-
Theodore and Gendelman [35] (*n*= 33)	13 (39)	4 (12)	18 (55)	3 (9)	1(3)	-	10 (30)	-
Hitchins et al. [65] (*n*= 44)	21 (48)	7 (16)	13 (30)	-	4 (9)	2 (3)	3 (4)	-
Kaplan et al. [20] (*n*= 63)	20 (32)	-	40 (63)	-	9 (14)	-	-	-
Freilich et al. [66] (*n*= 77)	10 (13)	3 (4)	13 (17)	-	4 (5)	2 (3)	3 (4)	-
Chamberlain [28] (*n*= 61)	14 (23)	-	-	-	-	-	-	-
Wasserstrom et al. [19] (only solid tumours) (*n*= 90)	30 (33)	10 (9)	15 (17)	2 (2)	5 (6)	2 (2)	2 (2)	2 (2)
Yap et al. [21] (breast cancer) (*n*= 25)	13 (52)	8 (32)	11 (40)[b]	-	2 (8)	6 (24)	2 (8)	-
Griffin et al. [10] (lymphoma) (*n*=21)	8 (38)[a]	-	-	-	-	-	-	-
Levitt, et al. [11] (non-Hodgkin's lymphoma) (*n*=24)	2 (8)	-	-	-	-	-	-	-

[a] Including headache alone

[b] Delirium

leukaemia, lymphomas and breast carcinoma metastases with direct chiasma or optic nerve invasion [82, 83]. Blindness from meningeal carcinomatosis may rarely be confused with the effects of chemotherapy [84]. Uncommonly, the first complaint is tinnitus, hoarseness, dysphagia, vertigo, or a decrease in taste [19]. Vertigo and hearing loss mimicking Meniere's syndrome can develop in neoplasms involving cochlea and labyrinth, sometimes bilaterally [85-87].

Cranial nerve abnormalities (Table 7) [10, 11, 19-21, 23, 28, 29, 35, 66] are frequently shown by a neurological exam. Usually, more than one cranial nerve is involved [88], often bilaterally at variance with base of the skull tumours [1]. Ophthalmoparesis is the most frequent finding [19, 20]; it may be limited to only one oculomotor nerve [89], but a more common finding is multiple nerve palsy, due to tumoural invasion of the cavernous sinus [1]. Peculiarly, ocular movement disturbances may not provoke dyplopia [1]. Facial weakness is frequently seen [19, 20], sometimes in the form of unilateral facial palsy mimicking Bell's palsy [90]. Also frequently observed are decreased hearing, optic neuropathy, trigeminal neuropathy and hypoglossal neuropathy. Less commonly, neurologic examinations show blindness and abnormal gag reflex (Table 7).

Myeloradicular symptoms and signs are seen in the majority of patients (Tables 8 and 9) [10, 11, 19-21, 23, 28, 29, 35, 65, 66]. Sometimes, radicular deficits are the only complaint of leptomeningeal metastases [20, 91]. The most frequent symptoms are weakness, more frequently in the lower limbs, paraesthesia in one or more extremities, instability of gait, radicular pain, pain in the neck or back, and bladder or bowel dysfunction [19, 20, 23, 29, 67]. Gait difficulty origi-

Table 5 Cerebral signs in leptomeningeal carcinomatosis at the time of diagnosis

Reference	Cases with cerebral signs, *n* (%)			
	Cognitive impairment	Ataxic gait	Papilloedema	Hemiparesis
Olson et al. [23] (*n*= 50)	26 (52)	18 (36)	-	-
Little et al. [29] (*n*= 29)	13 (45)	-	-	-
Theodore and Gendelman [35] (*n*= 33)	15 (45)	12 (36)	7 (21)	2 (6)
Kaplan et al. [20] (*n*= 63)	29 (48)[a] 20 (31)[b]	14 (22)	-	-
Chamberlain [28] (*n*= 61)	3 (5)	-	-	-
Wasserstrom et al. [19] (only solid tumours) (*n*= 90)	28 (31)	12 (13)	5 (6)	1 (1)
Yap et al. [21] (breast cancer) (*n*= 25)	-	-	8 (38)[d]	-
Griffin et al. [10] (lymphoma) (*n*=21)	14 (56)[c]	-	5 (20)	-
Levitt, et al. [11] (non-Hodgkin's lymphoma) (*n*=24)	3 (12)	-	-	-

[a] Confusion
[b] Lethargy
[c] Disorentation
[d] Including headache alone

Table 6 Cranial nerve symptoms in leptomeningeal carcinomatosis at the time of diagnosis.

Reference	Cases with cranial nerve symptoms, *n* (%)							
	Diplopia	Hearing loss	Facial numbness	Impaired vision	Decreased taste	Tinnitus	Dysphagia	Vertigo
Olson et al. [23] (*n*= 50)	12 (24)[a]	-	-	-	-	-	-	-
Little et al. [29] (*n*= 29)	19 (66)[a]	-	-	-	-	-	-	-
Theodore and Gendelman [35] (*n*= 33)	26 (79)[a]	-	-	-	-	-	-	-
Hitchins et al. [65] (*n*= 44)	2 (4)	1 (2)	-	-	-	-	-	-
Kaplan et al. [20] (*n*= 63)	26 (41)[a]	-	-	-	-	-	-	-
Freilich et al. [66] (*n*= 77)	7 (9)	-	3 (4)	3 (4)	-	-	2 (3)	-
Wasserstrom et al. [19] (only solid tumours) (*n*= 90)	18 (20)	7 (8)	5 (6)	5 (6)	3 (3)	2 (2)	1 (1)	1 (1)
Yap et al. [21] (breast cancer) (*n*= 25)	6 (24)	6 (24)	-	9 (36)	-	2 (8)	-	-

[a] Cranial nerves not otherwise specified

Table 7 Cranial nerve signs in leptomeningeal carcinomatosis at the time of diagnosis

Reference	Cases with cranial nerve signs, *n* (%)							
	Ophthalmo-paresis	Optic neuropathy	Facial weakness	Hearing loss	Trigeminal neuropathy	Hypoglossal neuropathy	Blindness	Abnormal gag reflex
Olson, et al. [23] (*n*= 50)	39 (78)[a]	-	-	-	-	-	-	-
Little et al. [29] (*n*= 29)	21 (72)[a]	-	-	-	-	-	-	-
Theodore and Gendelman [35] (*n*= 33)	13 (39)	7 (21)	10 (30)	1 (3)	6 (18)	10 (30)[b]	3 (9)[c]	-
Kaplan et al. [20] (*n*= 63)	31 (40)[a]	-	-	-	-	-	-	-
Freilich et al. [66] (*n*= 77)	7 (9)	-	8 (10)	-	3 (4)	1 (1)	3 (4)	2 (2)
Chamberlain [28] (*n*= 61)	21 (34)[a]	-	-	-	-	-	-	-
Wasserstrom et al. [19] (only solid tumours) (*n*= 90)	18 (20)	5 (6)	15 (17)	9 (10)	5 (6)	5 (6)	3 (3)	3 (3)
Yap et al. [21] (breast cancer) (*n*= 25)	11 (44)	-	6 (24)	6 (24)	-	-	-	-
Griffin et al. [10] (lymphoma) (*n*=21)	11 (52)[a]		-	-	-	-	-	-
Levitt et al. [11] (non-Hodgkin's lymphoma) (*n*=24)	17 (71)[a]	-	-	-	-	-	-	-

[a] Cranial nerves not otherwise specified

[b] With dysarthria, dysphagia and hoarseness

[c] Hemianopsia

nates from sensory motor deficits and cerebello-vestibular alterations in both brain and myeloradicular involvement. Its characteristics depend on the prevalence of leg weakness, spasticity, and ataxia; in several cases it appears as gait apraxia [92].

Radicular pain may mimic the symptoms of radiculopathy due to an herniated vertebral disk [1]. When back pain, sometimes associated with nuchal rigidity, is the only complaint, it may be difficult to distinguish LMD from meningitis. Back pain can be the only symptom before the onset of other neurological findings. LMD should be suspected when back pain is not explained by other causes such as bone metastases to the spine or epidural metastases. The most frequent bowel or bladder dysfunction is insensitivity to fullness, with enlargement of the bladder [1, 20].

More than two-thirds of patients have signs of spinal root involvement on initial examinations, principally tendon reflex asymmetries and Lasègue's sign (Table 9) [19, 20, 23, 29, 65].

Laboratory findings

Occasionally the diagnosis of LMD can be accepted on the basis of clinical criteria alone: when a patient is affected by a known cancer and presents unequivocal signs of more than one level of central nervous system involvement in the absence of any other clinical or radiological explanation for neuraxis dysfunction. It is, however, rare to find clinical signs of meningeal carcinomatosis without abnormalities at radiological or cerebrospinal fluid (CSF) examinations.

Cerebrospinal fluid examination

CSF examination is the single most important diagnostic test for LMD [19, 20, 93, 94] and should therefore be performed in every patient with suspected LMD. The presence of cerebral tumoural masses should be considered to avoid the risk

Table 8 Myeloradicular symptoms in leptomeningeal carcinomatosis at the time of diagnosis

Reference	Cases with myeloradicular symptoms, *n (%)*				
	Weakness	Paraesthesia numbness	Radicular pain	Pain in neck or back	Bladder/bowel dysfunction
Olson et al. [23] (*n*= 50)	11 (22)	5 (10)	12 (24)[a]	-	1 (2)
Little et al. [29] (*n*= 29)	8 (28)	12 (41)	10 (35)[a]	-	1 (3)
Theodore and Gendelman [35] (*n*= 33)	20 (60)	11 (33)	8 (24)[a]	-	-
Hitchins et al. [65] (*n*=44)	16 (36)	9 (20)	14 (32)[a]	-	2 (4)
Kaplan et al. [20] (*n*= 63)	24 (38)	19 (30)	37 (58)	11 (18)	12 (19)
Freilich et al. [66] (*n*=77)	17 (22) -	6 (8)[b] 3 (4)[c]	12 (16)[b] 1 (1)[c]	15 (19) -	6 (8) -
Wasserstrom et al. [19] (only solid tumours) (*n*= 90)	34 (38)	31 (34)	19 (21)	23 (26)	12 (13)
Yap et al. [21] (breast cancer) (*n*= 25)	1 (4)	-	-	4 (16)	5 (20)
Griffin et al. [10] (lymphoma) (*n*=21)	2 (9)	2 (9)	2 (9)	1 (5)	-

[a] Pain type not specified
[b] Limbs
[c] Perineum

of herniation. Also, acute epidural spinal cord compression has been precipitated by lumbar puncture below an unknown metastatic epidural lesion. The first lumbar puncture is abnormal in some respect in 97% of patients, while a repeated CSF exam will disclose abnormalities in 99% of patients after the third trial [19].

At the beginning of the manoeuvre, CSF pressure is above 16 cm H_2O in about half of patients, keeping a lateral recumbent position [19]. Increased cerebrospinal fluid pressure often occurs without evidence of hydrocephalus in imaging studies [1]. Other causes of cerebrospinal fluid hypertension should be ruled out. Indirect signs of intracranial hypertension are not often reliable [95]. The cell count is elevated to above 5 cells/mm^3 in more than half of patients, with a majority of lymphocytes, even if polymorphonuclear leukocytes can be found [19, 20]. Occasionally hundreds of leukocytes are observed, raising the suspicion of infection [1]. Eosinophilia in cerebrospinal fluid is a common clue in lymphomas and may direct the diagnosis [96, 97]. Both basophilic and eosinophilic meningitis were seen in a patient affected by meningeal leukaemia [98]. However, CSF eosinophilia is also found in patients treated with ibuprofen, an analgesic frequently used in cancer pain therapy [99]. Xantochromia and erythrocytes are sometimes found as a consequence of meningeal invasion and bleeding tumours, particularly frequent in the case of melanoma [1]. True subarachnoid haemorrhage is rarely seen [100]. Melanoma may release melanin that gives a black colour to the cerebrospinal fluid [1].

If clinical findings strongly suggest meningeal carcinomatosis, a diagnosis may be made in patients with negative cytology by relatively non-specific abnormalities, such as hypoglycorrachia or elevated CSF proteins (greater than 100 mg/dl). Protein concentration is often high, due to both a blood-brain barrier lesion and direct tumoural production [1]. In lymphoma and leukaemia, cerebrospinal fluid proteins are increased in a minority of patients [20]. Protein concentration is lower in ventricular CSF than in cisterns and lumbosacral sac CSF [1]. The presence of IgM in the CSF is pathognomonic of intrathechal production, since they do not pass a relatively intact blood-brain barrier [101]. An increase of IgG index or oligoclonal immunoglobulin bands, suggesting an intrathechal immunoglobulin production, has been found in 8 of 22 patients with leptomeningeal metastases from various tumours [102]. Elevated myelin basic protein is another frequent clue in LMD [103, 104]. The prognostic value of a high protein level and its decrease after chemotherapy is doubtful [13, 19, 105].

Hypoglycoracchia is revealed by a lumbar puncture in about half of patients [19, 20, 106]. CSF glucose level is dependent on serum glucose levels but, since the latter may change quickly, measurement of glycemia may not give a precise indication and so it is preferred to refer to glucose levels above 40 mg/dl as normal [1]. Glycorrhachia is not related to the number of cells found in CSF examination [1], but low glucose levels in cerebrospinal fluid are considered to parallel tumour extension and have been correlated with poor prognosis [13, 19, 105].

Table 9 Myeloradicular signs in leptomeningeal carcinomatosis at the time of diagnosis

Reference	Cases with myeloradicular signs, *n* (%)						
	Abnormal reflexes	Motor deficit	Sensory deficit	Cauda equina signs	Lasègue signs	Decreased rectal tone	Nucal rigidity
Olson et al. [23] (*n*= 50)	30 (60)	39 (78)	25 (50)	-	-	-	-
Little et al. [29] (*n*= 29)	24 (27)	20 (69)	15 (51)	-	-	-	-
Theodore and Gendelman [35] (*n*= 33)	8 (24)	18 (54)	11 (33)	-	-	-	11 (33)
Kaplan et al. [20] (*n*= 63)	-	27 (47)	23 (37)	-	-	-	-
Chamberlain [28] (*n*= 61)	16 (27)[a] 5 (9)[b] 7 (12)[c]	-	-	16 (27)	-	-	-
Wasserstrom et al. [19] (only solid tumours) (*n*= 90)	64 (71)	54 (60)	24 (27)	-	11 (12)	10 (11)	7 (8)
Yap et al. [21] (breast cancer) (*n*= 25)	3 (12)[d]	7 (28)	2 (8)	-	4 (16)	-	2 (8)
Griffin et al. [10] (lymphoma) (*n*=21)	-	3 (14)[e]	-	-	-	-	-
Levitt et al. [11] (non-Hodgkin's lymphoma) (*n*=24)	5 (21)[f]	-	-	-	-	-	-

[a] Ataxia
[b] Root signs
[c] Cord signs
[d] Absent reflexes
[e] Cord compression
[f] Myeloradicular involvement not otherwise specified

The presence of tumoural cells in the CSF is the definite proof of LMD [93, 106-108]. Positive cytological results are found at initial lumbar puncture (LP) in 50% of patients, at the second lumbar puncture in 25% of patients, and at subsequent LPs in an additional small percentage. CSF is persistently negative for tumoural cells in about 10% of patients [19, 20, 93, 109]. Negative search for tumour cells in the CSF can be more common with leukaemia and lymphoblastic neoplasm than with carcinomas [19, 93]. Occasionally, tumoural cells are found in asymptomatic patients [56]. The number of cells found in a CSF examination does not relate to the tumour burden infiltrating the leptomeninges [1]. However, it has been reported that the wider is the tumoural spread, the more frequent is a positive exam for tumoural cells in the CSF [93]. Tumoural cells are more frequently found with a lumbar puncture than in the cerebroventricular spaces, and consequently this approach is preferred at the beginning and in subsequent evaluations [93, 110, 111]. The cytocentrifuge technique improves CSF cytological examinations [112], as does use of a Millipore filter [20, 107, 113, 114]. A minimum of 4 cc CSF should be sent to the laboratory to optimise cell finding [1].

Recently, utilisation of labelled monoclonal antibodies directed to tumoural cells has increased the sensitivity of CSF metastatic cell findings [115, 116]. Use of techniques such as polymerase chain reaction and Southern blot analyses for gene rearrangements [117] will probably improve the detection of tumoural cells in CSF.

A few recent studies report an improvement in detecting CSF tumoural cells with flow cytometry [118, 119]. Cell abnormalities recognised by flow cytometry, strongly suggesting LMD, are nuclear absence or nuclear multiplicity [1]. One report suggests the utility of chromosomal analyses in the diagnosis of LMD from lung cancer [120].

The possibility of false positive results is due to the detection of lymphocytes in lymphoma, which are difficult to distinguish from nonspecific inflammatory cells [56, 93, 121, 122]. Unfortunately, inflammation and reactive lymphocytes often coexist with LMD in lymphoma [123-124]. In older studies, tumoural cells were found in the CSF of patients affected by brain metastases, but not by meningeal carcinomatosis, in 20%-40% of cases [126]. Posner and colleagues do not agree with this view and suggest that this situation only occasionally occurs [1, 93].

Occasionally, leptomeningeal biopsy may help to confirm the diagnosis of LMD [127], but nowadays a blind biopsy does not guarantee that the metastases localisation is catched. Endoscopical guide provides an intriguing possibility to localise the meningeal biopsy [128].

A positive match with monoclonal antibodies may confirm a diagnosis in those cases of negative cytology [129-131]. Monoclonal antibodies directed to surface tumoural antigens increase by 9% the sensitivity of detecting neoplastic cells in the CSF [1]. This technique is particularly useful to distinguish monoclonal lymphocyte cells of lymphoma from inflammatory polyclonal leukocytes [1].

Several biochemical markers have been studied to improve the sensitivity of CSF examination for LMD diagnosis [132-136]. Carcinoembryonic antigen (CEA) is elevated (above 100 ng/ml) in the CSF of 63% of patients, in spite of a serum CEA below 100 ng/ml [19, 137, 138]. Cerebrospinal fluid CEA has diagnostic value when it is more than 1% of serum CEA [1]. It is increased in 75% of patients with breast cancer, in 60% with lung cancer, and in 100% with melanoma, while it is normal in cases of leptomeningeal carcinomatosis from lymphomas [19, 138]. Human chorionic gonadotropin is detected in the CSF in choriocarcinoma, embryonal carcinoma and germ cell tumours infiltrating leptomeninges [1]. Alpha-fetoprotein increases in the CSF of patients with LMD from teratocarcinoma, yolk sac tumour, endodermal sinus tumour or embryonal carcinoma [1]. Prostate-specific antigen may be elevated in prostate cancer metastases to leptomeninges [139]. Cerebrospinal fluid CA-125 is found in ovarian carcinoma and CA 15-3 in breast cancer [1]. Detection of 5-hydroxyindoleic acid (5-HIAA) in the CSF is diagnostic for carcinoid meningeal metastases [48]. High molecular weight epithelial-associated glycoprotein antigen (HMFG1) has been reported in meningeal carcinomatosis but not in meningitis [115]. Galactotransferases are associated with leukaemia and lymphoma leptomeningeal metastases [140].

Cerebrospinal fluid β_2-microglobulin increases (above 2 mg/l) in haematological leptomeningeal metastases but also in infections, and is therefore not specific [141-144]. β-Glucuronidase above 80 mU/l in CSF strongly suggests the presence of leptomeningeal metastases [138, 145, 146]. This marker is positive in two-thirds of patients with carcinoma of the lung and breast and with melanoma, but it is usually only slightly elevated in lymphoma leptomeningeal invasion [9, 138, 142]. A decrease in β-glucuronidases is observed after meningeal carcinomatosis therapy, giving additional information on therapeutic response [138, 145]. The measure of lactate dehydrogenase (LDH) in CSF has low sensitivity for LMD [132]. However, abnormal isoenzyme patterns (with an LDH: isoenzyme V greater than 15%) occur in the CSF of 75% of patients [19, 133, 147]. Often observed is an elevated level of CSF lactate (its levels are inversely correlated to the CSF glucose levels), suggesting that the lactate levels simply reflect increased tumour glycolyses in the leptomeninges and spilling of lactate (the end-product) into the CSF [19]. β-Glucuronidase, lactate and β_2-microglobulin are also elevated in patients suffering from inflammatory diseases of leptomeninges [138, 141, 145, 147], while CEA and the 5:1 LDH-isoenzyme ratio are abnormal exclusively in cancer patients [147]. Increased CSF alkaline phosphatase concentration has been reported in cases of meningeal carcinomatosis from lung tumours [148]. Cerebrospinal fluid ferritin is elevated in most studies both in meningeal carcinomatosis and in inflammatory meningitis [149, 150]. Glucosephospate isomers [151], myelin basic protein [104, 152] and tissue polypeptide antigen [153] are also increased in the CSF of patients with LMD.

Levels of tumour markers on the first examination are not important for prognosis [121], but their variations have been used in some cases to follow-up the evolution of leptomeningeal carcinomatosis and response to therapy [132, 138, 142].

Neurophysiological exams

Electromyography and nerve conduction studies can demonstrate radicular tumoural invasion. In a set of 10 patients with leptomeningeal carcinomatosis and radicular disturbances, Kaplan et al. [154] found abnormal needle electromyography in 60%-100% of patients (with respect to the region examined), and a slowing or decrease of motor or sensory activity potential amplitude in nerve conduction studies of lower limbs in 66%. Interestingly in 3 of 5 patients, myelography was normal and in 3 of 10 patients a tumour was not suspected before electromyography exam. On the other hand older electromyography electroneurography studies describe a low sensitivity in peripheral nerve involvement from metastases [155].

Triphasic waves, typically seen in metabolic brain diseases, were described in electroencephalographic exam of a patient affected by meningeal carcinomatosis and brain tumoural invasion [78].

Imaging studies

Two findings revealed by computed tomography (CT) or magnetic resonance imaging (MRI) strongly suggest

meningeal metastasis: a meningeal contrast enhancement and an enlargement of ventricle or sulci. Enhancement reflects a blood-brain barrier lesion and may be seen both in cerebral and spinal regions (Fig. 1), but false negative exams are frequent, even with more sensitive MRI scanners [156-159]. Less frequently seen is a true meningeal thickening in the spinal cord, with its so-called sugar-coated appearance (Fig. 2) [157, 160, 161] or with subarachnoid nodules (Fig. 3) [28]. These aspects are not specific, since they may also be observed in all inflammatory lesions of the leptomeninges. Neuroradiological exams seem less sensitive in adults than in children [28, 54].

In the cranial region, enhancement by radiographic contrast is seen in 16%-39.7% of patients (Fig. 4). Com-municating hydrocephalus, suggesting obstruction of liquoral pathways, is revealed by CT in 8%-36.7% of patients (Fig. 5) [19, 20]. Better sensitivity values refer to more recent studies.

Nowadays, gadolinium-enhanced magnetic resonance strongly contributes to establishing the correct diagnosis and documening the extent of lesion [66, 162, 163]. MRI may reveal leptomeningeal metastases in patients with negative cytological exams of the CSF [28, 66]. MRI resonance is as sensitive as myelography-CT for studies in the spinal region; it also discloses abnormalities in about half of patients affected by leptomeningeal carcinomatosis, disregarding clinical signs [28]. However, MRI is preferable to a myelography-CT since it is not invasive and is better at revealing epidural spinal cord compression and intramedullary spinal

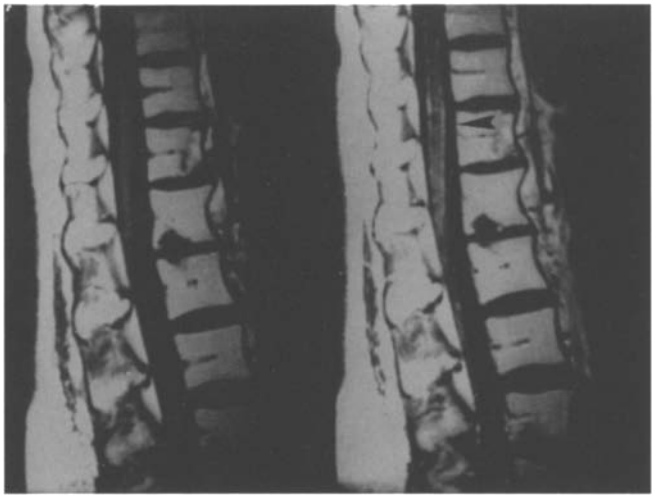

Fig. 1 Typical linear and dot-like contrast enhancement of lumbar meninges seen with MRI. *Left*, the pre-contrast image. *Right*, the *arrow head* lies anteriorly to the subaracnoidal space at the level of linear gadolinium meningeal enhancement. The patient had breast cancer and presented with bilateral lumbosacral radiculopathy. CSF examination was not performed due to patient refusal. The diagnosis of LMD was made on the basis of clinico-radiological findings and palliative radiation therapy was given to the lumbosacral region with good clinical effect

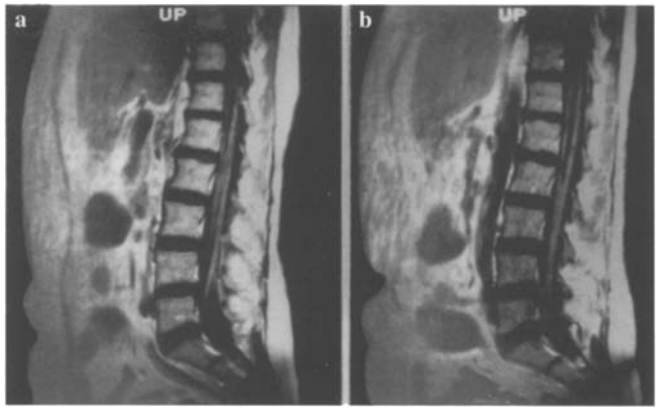

Fig. 2 MRI. Thick "sugar-coated" type of gadolinium enhancement on MRI images of cauda equina **a** and lumbar meningeal sac. **b** The patient had breast cancer and presented with focal lower back pain which went unrecognized for months before other neurological symptoms developed. (From [170] with permission of Oxford University Press)

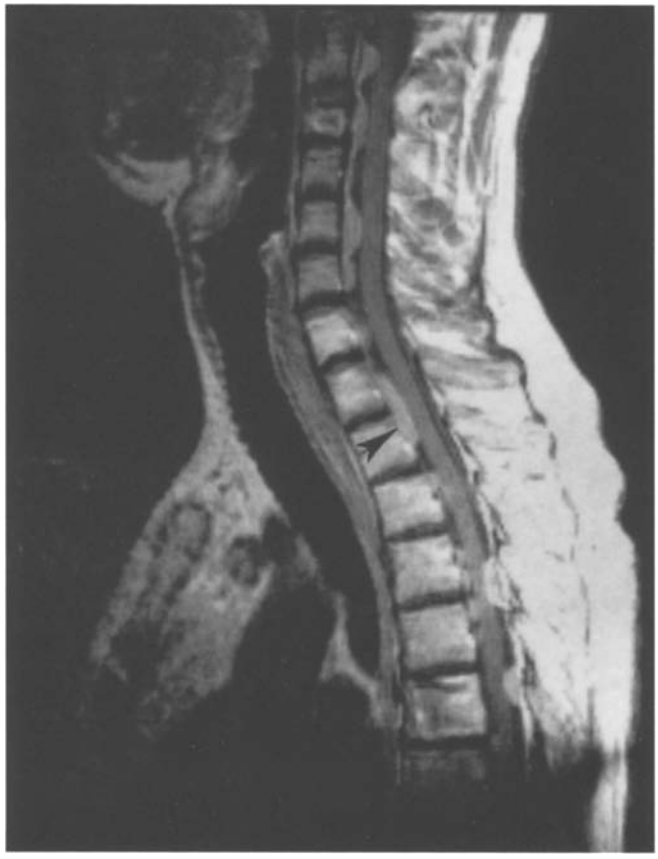

Fig. 3 Nodular enhancement on MRI image of cervicodorsal meninges in a case of lymphoma presenting with poliradicular findings in the upper and lower limbs. *Black arrow*, one of the biggest lesions

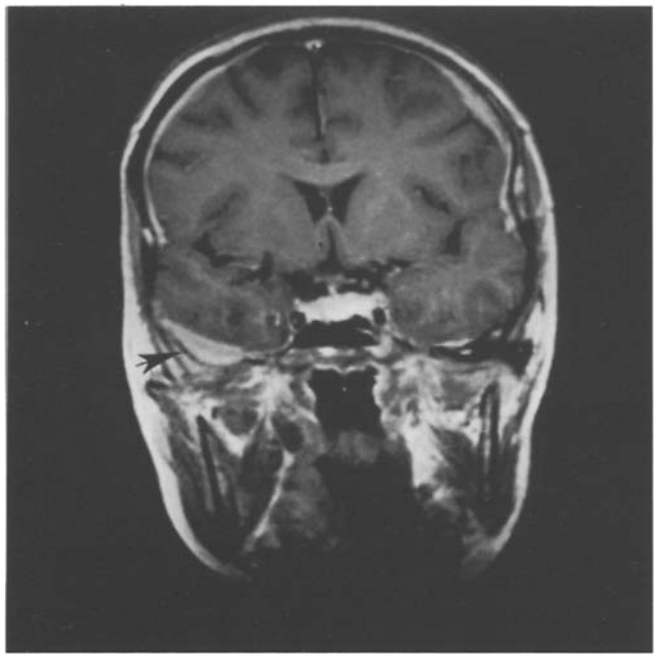

Fig. 4 Cerebral meninges involvement with evident MR enhancement and thickening of the base of the skull meninges (*black arrow*). The patient had head and neck tumour and developed neck pain with meningismus followed by multiple progressive cranial nerve involvement

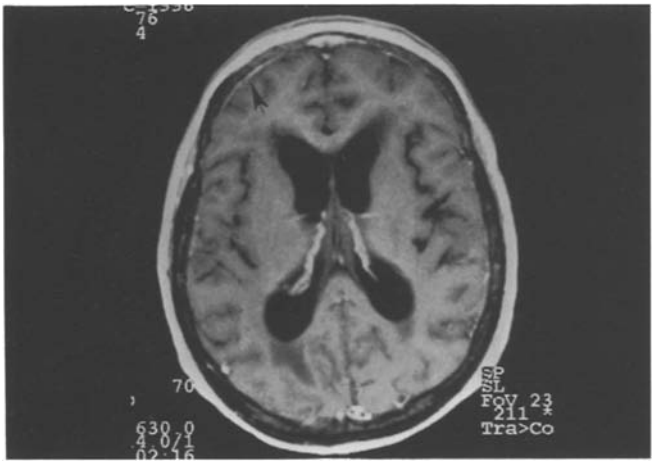

Fig. 5 MRI of patient with breast cancer. Communicating 4 ventricles hydrocephalus was found after rapid deterioration of cognition and vigilance. Functions recovered after CSF shunting. CSF examination revealed malignant cells. *Arrow*, linear meningeal enhancement of doubtful diagnostic meaning

cord and cerebral metastases (Fig. 6) [28]. Neoplastic invasion of cauda equina is also well demonstrated with MRI (Fig. 2) [66, 160].

Myelography is rarely positive for leptomeningeal tumour in patients with negative MRI exams [157].

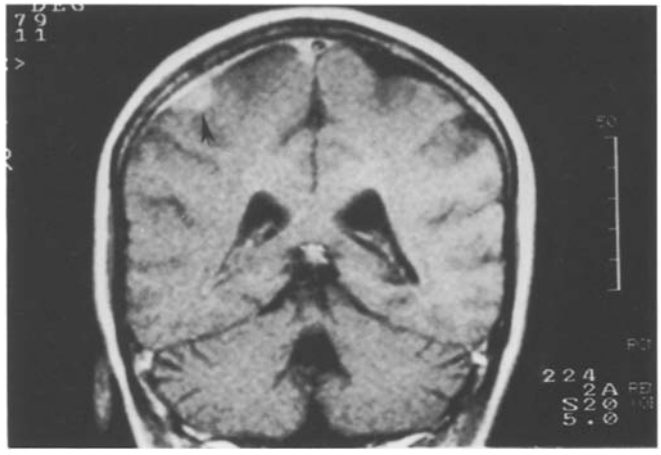

Fig. 6 MRI of patient with breast cancer. Diffuse meningeal enhancement with a meningeal nodule which is compressing and displacing the left posterior parietal cerebral cortex (*black arrow*). The patient had accessional episodes of paraesthesia and pain referred to the right upper limb which were interpreted as partial seizures

Myelography reveals leptomeningeal metastases in more than 50% of patients with spinal localisation; it shows a thickening and nodularity of nerve roots, principally at the cauda equina, in 25% of patients, and the signs of spinal epidural metastases in another 25% of patients [19, 164].

Occasionally, cerebral angiography helps to support a meningeal carcinomatosis diagnosis, showing the narrowing in diameter of multiple meningeal vessels [19, 165, 166].

CSF kinetic studies

Abnormalities of cerebrospinal fluid kinetics at ventriculography are seen in about 50% of patients in a few studies performed with indium-111-DTPA or technetium-99m-DTPA. These findings are aspecific and consist of ventricular and spinal obstructions and delays of CSF flow on the cerebral convexities [167-169]. The sensitivity of radionuclide CSF flow studies is actually superior to that of MRI or myelography-CT in disclosing CSF flow abnormalities [54]. However, new MRI CSF flow study techniques are promising. Since CSF compartmentalisation may obstruct intraventricular chemotherapy, according to some authors, a ventriculography should be obtained in all patients before starting this therapy [167-121].

Sommario *Gli Autori revisionano gli aspetti clinici e strumentali coinvolti nella diagnosi di diffusione meningea sia di tumori solidi che di leucemie o linfomi. Viene sottolineata l'importanza dell'associazione di reperti clinici, esame del*

liquor cefalorachidiano e dati radiologici per consentire una diagnosi precoce. La crescente prevalenza di questa complicazione del cancro disseminato richiede particolare attenzione da parte del neurologo impegnato nella consultazione in medicina generale e in oncologia.

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ERRATUM

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Predictive testing for Huntington's disease: ten years' experience in two Italian centres

Ital J Neurol Sci (1998) 19:68-74

Owing to an error the name of Prof. Giovanni Abbruzzese was missing. The co-Authors and the publisher apologize for any inconvenience.