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CEREBROSPINAL FLUID CYTOMORPHOLOGIC FINDINGS IN 41 INTRACRANIAL TUMORS

A RETROSPECTIVE REVIEW

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SUMMARY - The main objective of this retrospective review of clinical and cerebrospinal fluid (CSF) data from 41 patients with intracranial tumors diagnosed between 1975 and 1989, is to report the role that the finding of neoplastic cells in CSF plays, specially when cerebral CT-scanning and MRI were not currently done. Another objective is to study the CSF proteic abnormalities in cerebral tumors. CSF cell count, cytomorphologic pictures obtained after sedimentation and protein findings are described. Tumor cells were seen in 12 cases (29%): medulloblastomas - 6, meningeal carcinomatosis - 3, multiforme glioblastoma - 1, ependymoma -1, cerebral metastasis -1; in two cases it was an unexpected finding. We noticed that tumoral localization next to the ventricles favoured cell exfoliation. Although pleocytosis was rare and uncorrelated with the presence of neoplastic cells, pathological cytomorphologic pictures appeared in most of the cases including all "positive" ones. Our results stress that the appearance of neoplastic cells in CSF remains helpful specially when it is an unexpected finding.

KEY WORDS: CSF cytology, CSF tumor cells, cerebral tumors.

Alterações citomorfológicas do líquido céfalo-raquidiano em 41 doentes com tumores intracranianos: estudo retrospectivo

RESUMO - O objectivo fundamental desta revisão retrospectiva dos dados clínicos e do estudo do líquido céfalo-raquidiano (LCR) de 41 doentes com tumores intracranianos diagnosticados entre 1975 e 1989 é analisar a importância do achado de células neoplásicas no LCR, principalmente quando o recurso à tomografia computorizada e ressonância magnética cerebrais era raro. Outro objectivo diz respeito ao estudo das alterações proteicas do LCR nos tumores cerebrais. A análise do LCR compreendeu a contagem celular, a observação dos quadros citomorfológicos obtidos após sedimentação, o doseamento das proteínas totais e a determinação dos perfis electroforéticos. Encontraram-se células tumorais em 12 doentes (29%): meduloblastomas - 6, meningites carcinomatosas - 3, glioblastoma multiforme - 1, ependimoma -1, metástases cerebrais -1; em 2 casos este achado foi inesperado. Na maior parte dos casos a localização do tumor perto do sistema ventricular favoreceu a exfoliação celular. Embora a pleocitose fosse rara e não se correlacionasse com a presença de células neoplásicas, verificámos que na maioria dos casos, incluindo todos aqueles com citologia "positiva", os quadros citomorfológicos eram patológicos. Os nossos resultados mostram que a pesquisa de células tumorais no LCR continua a ser util e o seu achado particularmente relevante quando inesperado.

PALAVRAS-CHAVE: citologia do LCR, células tumorais no LCR, tumores cerebrais.

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Since the beginning of this century many studies were published regarding the presence of neoplastic cells in cerebrospinal fluid (CSF) in different types of intracranial neoplasms. The significance of this finding was, therefore, thoroughly discussed [2, 11-14, 20, 25]. Although the diagnosis of cerebral tumors is nowadays settled by neuroradiological examinations, there are still several reasons that enhance the importance of searching tumor cells in CSF to detect primary neoplasms or metastatic involvement of the central nervous system (CNS). For instance, from a diagnostic point of view, cytomorphologic examination of the CSF may give a valuable contribution to the initial diagnosis of neoplastic pathology as happens in meningeal carcinomatosis where it represents a major tool[2]. Besides, it is particularly helpful to diagnose tumor recurrences which are often difficult to evaluate only by neuroradiological studies due to the superimposed changes of nervous structures provoked by postoperative radiation and chemotherapy[2, 11] . Moreover, the larger life expectancy of patients with systemic malignancies increases the incidence of neurological involvement and imposes thenceforth a precocious detection in order to allow more accurate therapeuthic approaches[27, 28]. On the other hand, this study also has therapeutic applications, since serial CSF cytologic examinations may be of great help to monitor the responses to therapeuthic measures directed to malignant leptomeningeal seeding[2, 18]. Furthermore, the unexpected finding of tumor cells in the CSF in patients not known for harbouring malignant tumors, specially when cerebral neoplasms are concerned and neuroradiological studies are not conclusive, is certainly of utmost interest and gives to the cytomorphological CSF study an overwhelming diagnostic value. Several authors have also described the cytomorphologic reactions disclosed by the presence of tumor cells in the CSF[22] as well as the accompanying proteic and immunologic abnormalities[33].

Since 1975 the Laboratory of the Neurology and Neurosurgery Department of the Hospital S.João has been devoted to the CSF cytoproteic studies in several neurological diseases specially with an inflammatory or demyelinating character[24, 26, 30]. Moreover, the search of neoplastic cells in CSF was sometimes specifically requested. In this study we present our results on that field correlating clinical and laboratorial CSF features. To our knowledge this is the first Portuguese report on this subject.

MATERIALS AND METHODS

From 1975 until 1989 we examined 63 samples of CSF obtained from patients with a definite or suspected diagnosis of intracranial neoplasm. They had been sent to our Laboratory for the specific purpose of searching for neoplastic cells. They represent only 3% of the 2076 specimens of CSF that we received during that period. Six specimens were discarded for technical problems and 3 specimens from two patients in which neoplastic cells were found in CSF, despite unsuspected clinical malignancy, were also included. Therefore, 60 samples of 41 patients entered this study.

In 10 patients two or more CSF samples had been studied, but we considered only one sample per patient, choosing the first one when they were all negative or the one which presented tumor cells.

Clinical data included sex, age, definite diagnosis after histological study or probable diagnosis based only on clinical grounds and neuroradiological examinations in patients neither operated nor submitted to necropsy, tumor localization, purpose of CSF study and route of CSF collection.

CSF cell count was assessed using a Neubauer chamber. The CSF samples were prepared by a modified Sayk sedimentation method according to Oehmichen[21] and stained by the May-Grunwald Giemsa technique [7] as elsewhere described[26]. In a few cases other stainings were also performed, as the Papanicolaou, the Sudan Black B and the PAS stainings[7] but they did not improve the diagnostic accuracy. The usual criteria for malignant cells accepted in general cytology were considered[3, 15] taking a particular attention to those characteristics that allow their distinction from activated monocytoid cells, namely the higher nucleus-cytoplasmic ratio, nuclear and nucleolar abnormalities and the appearance of cell clumps.

In 15 cases total protein concentration was determined by a modified Lowry's method[23] and agarose gel electrophoresis of the concentrated CSF proteins was carried out and the electrophoretic patterns classified as previously described[29].

Table 1. Clinical and CSF laboratorial data of 41 patients with intracranial tumors.

Nr	Sex	Age Yr	Diagnosis		Tumor Localization	Purpose	Rotue	CSF				
								Tumor cells	Cell/mm3	Cytom. Reaction	Total Protein	Electroph. Pattern
1	M	22	Medulloblastoma	D	Cerebellum	Diagn.	V	+	11	Ly	n.d.	n.d.
2	M	3	Medulloblastoma	P	Cerebellum	Diagn.	V	-	0	Neut.	n.d.	n.d.
3	M	19	Medulloblastoma	D	Cerebellum	Ther.	L	+	2	Mix	0.23	N
4	F	3	Medulloblastoma	D	Cerebellum	Diagn.	V	-	n.d.	Mo	n.d.	n.d.
5	M	13	Medulloblastoma	D	Cerebellum	Ther.	L	+	24	Mix	n.d.	n.d.
6	F	17	Medulloblastoma	D	Cerebellum	Ther.	L	+	4	Ly	n.d.	n.d.
7	M	11	Medulloblastoma	D	Cerebellum	Ther.	L	+	0	Mix	n.d.	n.d.
8	F	12	Medulloblastoma	D	Cerebellum	Ther.	L	+	4	Mo	n.d.	n.d.
9	M	9	Astrocytoma	D	Cerebellum	Diagn.	L	-	114	Neut	0.4	N
10	F	26	Astrocytoma	D	Cerebellum	Diagn.	V	-	n.d.	N	n.d.	n.d.
11	M	16	Astrocytoma	D	Cerebellum	Ther.	L	-	20	Mix	n.d.	n.d.
12	F	19	Astrocytoma	D	Cerebellum	Ther.	V	-	0	Mo	n.d.	n.d.
13	F	8	Astrocytoma	D	Cerebellum	Ther.	L	-	0	Mo	n.d.	n.d.
14	M	28	Astrocytoma	D	Temporal lobe	Diagn.	L	-	0	Mo	0.63	T
15	F	1	Astrocytoma	D	Brainstem	Diagn.	V	-	n.d.	Mix	n.d.	n.d.
16	M	4	Astrocytoma	P	Brainstem	Diagn.	L	-	n.d.	Mo	n.d.	n.d.
17	M	10	Multif. glioblastoma	D	Brainstem	Diagn.	V	-	n.d.	Mo	n.d.	n.d.
18	M	45	Multif. glioblastoma	D	Temp/parietal	Ther.	L	-	4	Mix	n.d.	n.d.
19	M	54	Multif. glioblastoma	D	Parietal lobe	Ther.	V	-	2	Mix	n.d.	n.d.
20	M	37	Multif. glioblastoma	D	Peri-3rd vent.	Diagn.	L	+	13	Ly	2.6	T

M, male; F, female; D, definite; P, probable; Diagn, diagnosis; Ther, therapeutics.
V, ventricular; L, lumbar; Ly, lymphoid; Mix, mixed; Neut, neutrophilic; Mo, monocytoid.
N, normal; T, transudative; γ-Glo, gamma-globulinic; n.d., not determined.

Table 1. Clinical and CSF laboratorial data of 41 patients with intracranial tumor (cont.).

Nr	Sex	Age Yr	Diagnosis		Tumor Localization	Purpose	Rotue	CSF				
								Tumor cells	Cell/mm3	Cytom. Reaction	Total Protein	Electroph. Pattern
21	M	54	Cerebral metastasis	P	Bladder carc.	Diagn.	L	-	n.d.	Mo	n.d.	n.d.
22	M	44	Cerebral metastasis	P	Lung carc.	Diagn.	L	+	0	Mo	n.d.	n.d.
23	M	54	Cerebral metastasis	P	Lung carc.	Diagn.	L	-	0	Ly	n.d.	n.d.
24	F	33	Cerebral metastasis	D	Choriocarc.	Diagn.	L	-	5	Mo	n.d.	n.d.
25	M	54	Cerebral metastasis	P	Larynx car.	Diagn.	L	-	2	N	0.29	T
26	M	71	Cerebral metastasis	P	Cavum carc.	Diagn.	L	-	2	N	0.4	γ-Glo
27	F	35	Mening.carcinomatose	D	Gastric carc.	Diagn.	L	+	39	Ly	0.58	N
28	M	40	Mening.carcinomatose	P	Lung carc.	Diagn.	L	+	0	Mo	0.42	N
29	F	40	Mening.carcinomatose	P	Lung carc.	Diagn.	L	+	n.d.	Mix	n.d.	n.d.
30	F	37	Pituitary adenona	D	Pituitary	Diagn.	L	-	18	Mix	n.d.	n.d.
31	M	45	Pituitary adenona	D	Pituitary	Diagn.	L	-	22	Mix	0.46	T
32	M	22	Craniopharyngioma	D	Pituitary	Diagn.	L	-	0	Neut	0.27	N
33	M	46	Craniopharyngioma	D	Pituitary	Diagn.	L	-	18	Ly	0.32	N
34	M	50	Acoustic neuroma	D	Acoustic	Diagn.	L	-	0	N	1.55	T
35	F	57	Acoustic neuroma	D	Acoustic	Diagn.	L	-	0	Ly	3.1	T
36	F	47	Meningioma	D	Occipital	Diagn.	L	-	n.d.	Ly	n.d.	n.d.
37	F	9	Ependymoma	P	3rd Vent.	Diagn.	V	-	8	N	0.28	N
38	M	50	Ependymoma	P	Lateral vent.	Diagn.	V	-	1	Mix	n.d.	n.d.
39	M	11	Ependymoma	P	3rd Vent.	Diagn.	V	+	2	Mix	n.d.	n.d.
40	M	37	Glioma	P	Optic nerve	Diagn.	L	-	0	N	0.32	N
41	M	2	Retinoblastoma	D	Ocular	Diagn.	L	-	0	Mix	n.d.	n.d.

M, male; F, female; D, definite; P, probable; Diagn, diagnosis; Ther, therapeutics.
V, ventricular; L, lumbar; Ly, lymphoid; Mix, mixed; Neut, neutrophilic; Mo, monocytoid.
N, normal; T, transudative; γ-Glo, gamma-globulinic; n.d., not determined.

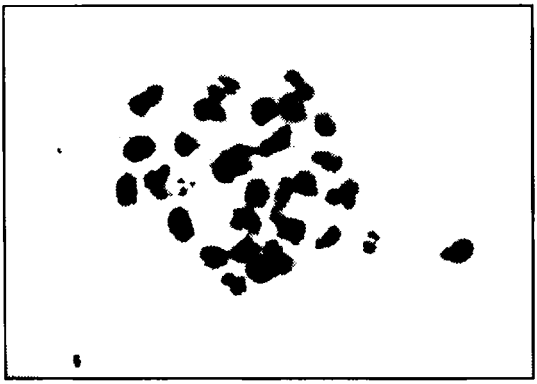

Fig 1. Patient 5. Medulloblastoma. A clump of medulloblasts with nuclear crowding and scanty basophilics cytoplasm is shown (May-Grunwald-Giemsa, x 600).

RESULTS

Clinical and laboratorial results from all patients are synopsed in Table 1.

A predominance of male sex (27 male; 14 female) and ages ranging from one to 71 years (mean = 28 years) was noticed. Distribution of ages according to the type of tumor was the expected one.

In all but two patients (Cases 20 and 28) the diagnosis was suspected by clinical and neuroradiological features. Histological confirmation was possible in 28 cases (68%); although a larger number of patients were submitted to surgery, in some cases only CSF shunt procedures were performed.

We verified that the CSF was mainly studied for diagnostic approach (31 cases - 76 %) and in most of the operated cases it was collected before surgery. Only in Cases 14, 15 and 36, the CSF was studied after surgery to clarify the diagnosis, because of a clinical suspicion of herpetic encephalitis following craniectomy in the first case and because of tumoral recurrence in the latter. Therapeutic programming, namely the decision of cranial radiotherapy and/or intrathecal chemotherapy, justified the CSF study after surgery in all the other cases (24%). We must stress that only in medulloblastomas postoperative therapeutic reasons more than diagnostic purposes impelled the CSF study.

The CSF was collected by lumbar puncture in 30 cases (73%) and by ventricular route in the other 11 patients (27%) who were submitted to external ventricular drainage.

Neoplastic cells were found in 12 cases (29%) with a special incidence in medulloblastomas (six, 79%) and in meningeal carcinomatosis (three, 100%). The other three cases comprised one multiforme glioblastoma situated next to the third ventricle, one supratentorial cerebral metastasis of a lung carcinoma and one ependymoma of the third ventricle. Only 4 of these 12 cases (33%) were not histologically confirmed: two patients with meningeal carcinomatosis, one patient with a metastatic lung carcinoma and another patient with a third ventricle ependymoma in whom clinical, neuroradiological and CSF examinations allowed the establishment of the diagnosis.

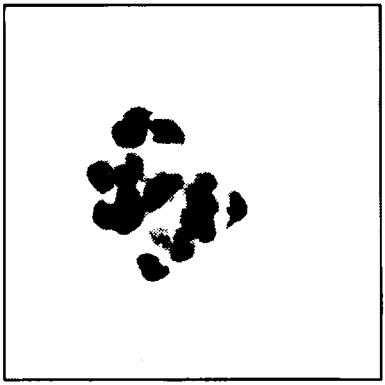

Fig 2. Patient 20. Multiforme glioblastoma. Notice the cellular clumping, pleomorphism, nuclear abnormalities, basophilic cytoplasm and ill-defined boundaries (May-Grunwald-Giemsa, x 600).

The predominant findings of each histological type of tumors are described as follows:

Medulloblastomas. In 7 out of 8 medulloblastomas the tumor was entirely excised by surgery and the CSF was usually collected afterwards. Medulloblasts were found in 6 cases (Fig 1) but cell count was usually normal.

Astrocytomas. Neoplastic cells were never observed in these tumors. Diagnosis was confirmed after surgery in all but one patient whose tumor localization at the brainstem prevented operation.

Multiforme glioblastomas. Four patients presented multiforme glioblastomas which, in 3 operated cases, was deeply located in the cerebral hemispheres. Only in Case

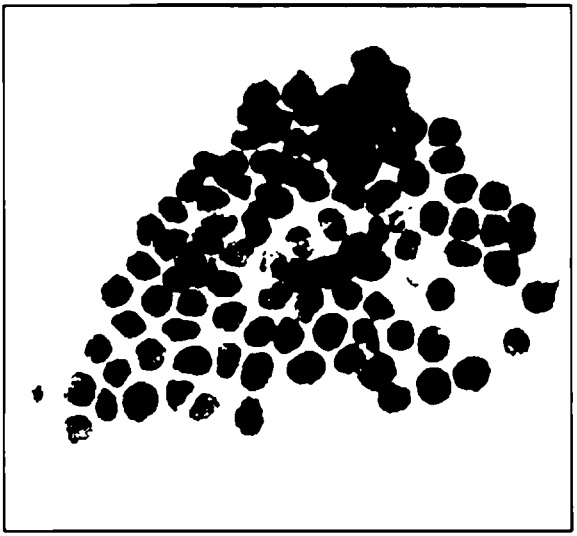

Fig 3. Patient 28. Meningal carcinomatosis from a squamous lung carcinoma. Pleomorphic cells with scanty cytoplasm and anysokariosis grouped in highly cellular clump are shown (May-Grunwald-Giemsa, x 600).

20 neoplastic cells were identified in the CSF as suggestive ofmalignant glioma (Fig 2). His CT-scan showed an hyperdense lesion adjacent to the third ventricle suggestive of inflammatory origin which justified a routine CSF study that disclosed its tumoral nature. Clinical situation rapidly deteriorated preventing surgery; necropsy studies disclosed a paraventricular multiforme glioblastoma.

Cerebral metastasis. In 9 patients metastatic involvement of the CNS either solid (6) or by meningeal carcinomatosis (3) was diagnosed. Histological confirmation was done in Case 24 and Case 27 by surgery and necropsy, respectively. In 4 cases, including all patients with meningeal carcinomatosis, neoplastic cells were present in the CSF. In Case 28 the unexpected finding of neoplastic cells (Fig 3) in a CSF sample collected when studying intracranial hypertension, led to the diagnosis of meningeal carcinomatosis; X-ray screening for primary tumor showed a lung carcinoma whose histology was not confirmed because his family did not allow the autopsy. The CSF sediment from Patient 22 with a cerebral metastasis presented clumps of small pleomorphic cells with features suggestive of oat cell lung carcinoma.

Other tumors. Twelve patients presented benign cerebral tumors and in eight cases surgical excision was performed. Cell count was high in four cases but neoplastic cells were found in only one patient. His tumor was localized in the third ventricle and it presented neuroradiological features suggestive of ependymomas; CSF was collected by ventricular puncture during a shunting procedure and tumoral biopsy was not done. Cells had characteristic features of ependymomas: isomorphism, anysokariosis and hyperchromatism.

Cell count, determined in 33 cases, was higher than 5/mm3 in only 10 cases (30%) distributed by all histological groups. No correlation between pleocytosis and the presence of neoplastic cells in CSF was found. Nevertheless, there was a pathological cytomorphologic picture in 35 cases (85%) also evenly distributed by all histological groups and which enclosed all "positive" cases, with a particular involvement of monocytoid (3 cases) or lymphoid (4 cases) cells sometimes associated to polymorphonuclear cells (5 cases).

As regards CSF protein study, we have found that in only 6 out of 15 cases the CSF total protein values were higher than 0.45 mg/dl and in 7 cases there was a pathological electrophoretic pattern usually of transudative type. In four cases with neoplastic cells where these studies were conducted we found normal values in two and pathological values in the remaining two cases.

COMMENTS

The identification of neoplastic cells remains one of the most important indications of CSF cytology. Nevertheless, several factors related either to the methodology of CSF processing or to the tumoral histology, make CSF cytology a rather difficult field of exfoliative cytology[2,28].

In this study we verified that the search for tumor cells in the CSF was requested to our Laboratory in only 63 instances during 15 years, which is a small number considering the totality of CSF samples studied in that period of time. This can be explained by the characteristics of our Hospital which is a General Hospital and not a specialized Cancer Institute; besides, we did not include hematological diseases with leptomeningeal seeding because those CSF samples are sent to the Hematology Department.

Except in medulloblastomas, the CSF study was usually done for diagnostic purposes and before surgery. This was expected taking in account that we included cases since 1975, that is, several years before CT-scanning was available in Porto, what may also explain the higher number of lumbar over ventricular CSF collections even in positive cases, which is in disagreement with the usual literature[2, 6, 7, 20].

The incidence of neoplastic cells in the CSF varies in the literature and is assumed to depend of several factors such as the predominance of metastatic tumors, the histological confirmation, the route of CSF collection, the kind of Hospital and the methodology of CSF processing[1, 3, 6, 7, 10, 11, 13, 21, 25, 28, 34]. Although our incidence of positive CSF cytology (29%) is a medium value comparing to those reported elsewhere, we may consider it lower than could be expected taking in account the high index of suspicion due to the specific request of searching tumor cells in those samples. We admit that false negatives may exist as has been largely reported in the literature[32] which may be explained by several reasons. At first, the sedimentation method that we prefer in accordance with a great number of cytologists[1, 2, 6, 8, 9, 15, 16, 31, 32] since it is more gentle and favors a better morphological preservation, leads to a loss of small cells contrasting to the filtration and cytocentrifugation techniques that get an higher number of cells; nevertheless detailed cell observation imposes sedimentation as the prefered screening method. Secondly, the retrospective nature of this review together with the widespread difficulty in the recognization of tumor cells in some cases, specially when clinical data is not provided, may both contribute to that low value[34]. In fact, neoplastic cells free in the CSF assume different characteristics from those seen in tissue sections . Moreover the frequent presence of an inflammatory reaction stimulated by meningeal tumoral dissemination[22] may difficult differential count as the activated monocytes and macrophages exhibit confusing characteristics and bizarre appearance[12, 22, 32, 33]. Cell identification may then be improved by immunocytochemical methods available in more specialized laboratories; nevertheless, in some cases as, for example, in meningeal carcinomatosis, immunocytochemistry was reported to be of minor help in reducing the number of false negative cytology[4] , so that it was pointed out that for screening procedures common cytomorphological methods should be prefered. Anyway we think that tumor cell identification in our cases was favored by good morphological preservation and some acquired experience in observing normal and inflammatory CSF cell pictures. This is emphasized by the clinically unexpected identification of neoplastic cells in two cases.

The relative distribution of positive cases according to the histology showed a predominance of medulloblastomas (50%) afterwards followed by meningeal carcinomatosis (25%), metastatic tumors (8.3%), multiforme glioblastomas (8.3 %) and ependymomas (8.3 %). This predominance of primary cerebral tumors over cerebral metastasis is different from other studies[1, 5, 7, 13, 14, 20, 21, 28] , and may be explained by the particular origin of our patients from a Department of Neurology and Neurosurgery . However, the higher rate of positivity we have found in meningeal carcinomatosis (100%) than in parenchymal metastasis from solid carcinomas (17%), in spite of the lower incidence of the former, is in agreement with other reports[3] . It is also well known that the detection rate in metastasis seems to improve with serial CSF studies[3, 5]; the fact that in only one case of cerebral metastasis more than one CSF sample (Case 24; 6 samples) was studied may in part explain that low value. As regards the primary tumor it is widely stated that, although the primary neoplastic source may never be discovered[3] , the lung is the most common neoplastic localization since Naylor's description[20] what is strenghtened by this study.

Our results of positive cytology in medulloblastomas and multiforme glioblastomas are in agreement with other studies pointing to the tendency for these lesions to spread in the CSF making its cytologic diagnosis eminently feasible[3]. We also verified that the relative distribution of positive cytology in primary cerebral tumors is in agreement with other series that included either all kinds of intracranial neoplasms or just the primary ones[1, 7, 11, 15, 21]. Tumor cells were not found in any case of astrocytoma, pituitary adenoma, craniopharyngioma, acoustic neuroma, meningioma, optic nerve glioma and retinoblastoma as is usually reported[15, 34].

We have also noticed that primary cerebral tumors that exfoliated cells to the CSF were all localized next to the ventricles. Thus, our results emphazise the role that some factors play in favouring the probability of finding tumor cells in the CSF, that were indicated before, such as the anatomic localization and the ability of cell exfoliation[5, 6, 12-14, 19, 20, 28, 34]. On the contrary, cells from tumors deeply localized in the cerebral parenchyma as happened in most cases of astrocytomas, multiforme glioblastomas and metastatic tumors were not found in the CSF.

We verified that the presence of neoplastic cells in CSF was not related to previous surgery, which gives support to other studies[7]. In our view, the importance that surgery plays in exfoliating cells to the subarachnoid space remains controversial.

The normal cell count found in most of our cases even in positive samples (seven cases) and when the CSF was collected after surgery was not a surprise since it had been reported before[7]. Notwithstanding, the most striking feature was the high incidence of pathological cell pictures, comprising all cases with neoplastic cells in the CSF, particularly with a mixed character or with a marked predominance of monocytes. These cellular reactions described in cerebral tumors are nonspecific[7] and may be in part explained by previous surgery[34] or intercurrent meningeal inflammation; besides, the disruption of the blood-brain-barrier (BBB) surely plays an important role in those reactions which is demonstrated by the increased total protein values and the transudative electrophoretic protein patterns of CSF found out in some cases. Other reports had already mentioned increased values of CSF total protein content in several kinds of cerebral tumors[7, 33]. Laterre[17] found in 70 cerebral and spinal tumors of different etiologies a transudative protein pattern which he related to intracranial hypertension and increased permeability of the BBB. The incidence of that pattern was in his studies largely higher than the incidence of degenerative or gamma-globulinic patterns in cerebral tumors[17]. Although these CSF cyto-proteic abnormalities are nonspecific, we agree with Van Zanten et al.[33] that little attention has been paid to the routine analysis of the CSF and to its relationship to the clinical data in tumoral pathology. In fact, it must be remembered that those kind of CSF cytoproteic abnormalities are not pathognomonic of infectious meningeal involvement.

In conclusion, we think that although CSF is nowadays seldomly collected in patients with cerebral tumors, cytological studies remain an important tool in the diagnosis of tumoral spread into the subarachnoid space. Besides, whenever a possibility of CSF collection emerges, routine biochemical and perhaps immunological analysis of the CSF shall also be done in order to better define the accompanying inflammatory picture.

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