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CLINICAL STUDY - PATIENT STUDY

Contribution of the daily melatonin profile to diagnosis of tumors of the pineal region

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Abstract Tumors of the pineal region (TPR) include different entities: germ cell tumors (GCT), pineal parenchymal tumors (PPT), meningiomas, and glial tumors. Except for GCT, there are no peripheral markers and histopathological diagnosis needs biopsy or surgery. We studied daily melatonin variations in twenty-nine patients with TPR and five with tectal plate glioma (TPG), used as controls, before and/or after surgery. Before surgery, a melatonin nycthemeral rhythm was observed in patients with TPG and TPR (one cyst, three PPT, one papillary tumor of the pineal region, two meningiomas, six gliomas). Melatonin rhythm was dramatically reduced for undifferentiated or invasive tumors. After surgery, the absence of melatonin variation in some cases could be the consequence of pineal damage by surgery. The contribution of determination of melatonin profiles to the diagnosis of TPR remains limited but of interest. The evidence for melatonin deficiency could justify melatonin administration to prevent the postpinealectomy syndrome.

Keywords Germ cell tumor · Melatonin rhythm · Pineal parenchymal tumor · Pineal region tumor · Papillary tumor of the pineal region

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Introduction

Melatonin secretion by the pineal gland is linked to the light–dark cycle, with an increase at night in all species, including humans [1]. Tumors of the pineal region (TPR) are rare and are composed of different entities: germ cell tumors (GCT), pineal parenchymal tumors (PPT), meningiomas, and glial tumors. Levels of human chorionic gonadotropin (hCG) and/or of its beta-subunit (β-HCG) and α-fetoprotein (AFP) can be elevated in patients with malignant GCT and help in the diagnosis of some of these tumors [2]. For the other types of TPR, there are no peripheral markers and histopathological diagnosis requires tumoral biopsy or surgery. The question of whether serum melatonin determination would be useful as a marker of pineal region neoplasms has repeatedly been raised [3–7]. In contrast with the situation in healthy subjects, in whom melatonin levels are low during the day and increase during the night [8], high daytime melatonin levels, again increasing at night, have been reported in a patient with a pineocytoma [4], the benign form of PPT, and in two

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patients with histologically unidentified pineal tumors [3, 6]. To date, the pattern of melatonin secretion in patients with a histologically identified TPR has only been reported in two studies, a series of nine tumors including four PPTs [9] and a series of thirteen tumors including five PPTs [7]. Only one of the patients presenting with PPT and one patient presenting with a germinoma displayed exaggerated melatonin production during the day. A physiological nycthemeral melatonin pattern was observed in patients presenting differentiated neoplasms but also in high-grade tumors [9]. In order to clarify the interest in investigating melatonin secretion in TPR, we studied daily melatonin variations before and/or after surgical tumor resection in twenty-nine patients with TPR of different well-defined histological types and in five patients with tectal plate glioma (TPG), as controls.

Materials and methods

Patients

The study included twenty-nine patients with TPR and five patients with tectal plate glioma (TPG), as controls. This tumor in the vicinity of the pineal region involves the same surgical approach (i.e. suboccipital transtentorial and supracerebellar infratentorial) but respects the integrity of the pineal gland. Table 1 summarizes the clinical data of the patients. The diagnosis was made in all patients by histological examination of specimens obtained during surgical removal of the tumor.

Morphological characterization of TPRs

Surgically removed tissues were fixed in 4% paraformaldehyde/15% picric acid or formol, embedded in paraffin, and cut into 4-µm sections. Histological examination of paraffin sections stained with hemalin–phloxin–saffron (HPS) was carried out at the Department of Neuropathology (Centre de Pathologie Est, Bron, France). Diagnosis and classification into histological subtypes were based on the World Health Organization (WHO) standard diagnostic criteria. All tumor specimens were studied using light microscopy and immunohistochemistry.

With the exception of those intended for testing for the presence of S100 protein, the sections were heated for 2×5 min in citrate buffer in a microwave oven, then stained with the specific antiserum. Immunohistochemical staining was performed using the avidin–biotin technique and either polyclonal antiserum against S100 protein (Dako, Trappes, France) or monoclonal antibodies against neuron-specific enolase (NSE, H14 Clone, Dako, Trappes, France), synaptophysin (SYN, SY38 Clone, Dako, Trappes, France), neurofilament (NF, 2F11 Clone, Dako, Trappes, France), chromogranin A (ChgA, Dak A3 Clone, Dako, Trappes, France), NeuN (A60 Clone, Chemicon, Euromedex, Mundolsheim, France), vimentin (VIM, V9 Clone, Dako, Trappes, France), glial fibrillary acidic protein (GFAP, 6F2 Clone, Dako, Trappes, France), epithelial membrane antigen (EMA, E29 Clone, Dako, Trappes, France), or cytokeratin (KL1 clone, Immunotech, Marseille, France).

Determination of the 24-h hormone melatonin profiles and data analysis

An indwelling catheter was inserted into an antecubital vein and 5-ml blood samples were collected every hour for 24 h under dim light (<50 lux). Samples were taken one or two days before surgery and several days after surgery. Plasma melatonin concentrations were determined by radioimmunoassay, according to a previously described procedure [10]. Sensitivity limit was routinely 5 pg/ml. A night/day variation was considered as significant when a nocturnal value was more than three times the day value. For one patient (case 1), urinary melatonin was also measured in samples taken during the day (7:00–19:00) and night (19:00–7:00). Written consent was obtained from all participants.

Results

Clinical data

The patients with tumors of the pineal region, regardless of the histology, presented with symptoms caused by increased intracranial pressure (ICP) or direct cerebellar or brain-stem compression. The clinical symptoms are listed in Table 1**.** ICP was observed in 28 cases. Headache, which occurs after obstruction of third ventricle outflow at Sylvius' aqueduct, was noted in six cases. More advanced hydrocephalus was associated with nausea, vomiting, and papilloedema. Somnolence and other cognitive deficits were observed in some cases. Direct brain-stem compression may lead to disturbances of extraocular movements, classically known as Parinaud's syndrome, and this occurred in 14 cases. Parinaud's features also include paralysis of upgaze or convergence, retractory nystagmus, and light-near papillary dissociation. Sleep wake-cycle disorders resulting mainly in vesperal sleepiness were noted after surgery in seven cases.

Morphological characterization of TPRs

The morphological data from HPS-stained sections and the characteristic immunolabelling of each type of TPR

Table 1 Clinical data, histological tumor type and melatonin rhythm in patients with tumors of the pineal region

Case	Tumor type	Age/Sex	Symptoms	MLT rhythm	
				Pre	Post
1	Pineal cyst	15/M	ICP/Parinaud syndrome	R	NR
2	Pineocytoma Grade I	64/F	ICP/Parinaud syndrome	NR	NR
3	Pineocytoma Grade I	26/M	Headache/Diplopy for bilateral abducens nerve palsy	R	NR
4	Pineocytoma Grade I	10/M	ICP/Vomiting/Vertigo	R	nd
5	Pineocytoma Grade I	54/M	ICP/Parinaud syndrome	R	nd
6	PPTID Grade III	50/F	Headache/Diplopy for unilateral abducens nerve palsy	NR	nd
7	PTPR	28/F	ICP/Hydrocephalus/Vomiting/Diminished visual acuity	R	nd
8	PTPR	67/M	ICP/Hydrocephalus/Headache	nd	NR
9	Oligodendroglioma grade III	25/M	ICP/Parinaud syndrome/Vertigo	R	NR
10	Pilocytic astrocytoma	3/M	ICP/Parinaud syndrome	R	nd
11	Pilocytic astrocytoma	32/F	Diminished visual acuity/Hydrocephalus/Vomiting	R	nd
12	Ependymoma grade III	22/F	ICP/Hydrocephalus/Vomiting	R	NR
13	Astrocytoma grade II	13/F	ICP/Parinaud syndrome/Diminished visual acuity	R	nd
14	Ganglioglioma	36/F	ICP/hydrocephalus/vomiting	R	nd
15	Germinoma	15/F	Headache/Diplopy for unilateral abducens nerve palsy	NR	nd
16	Germinoma	16/M	ICP/Parinaud syndrome	NR	nd
17	Germinoma	38/M	ICP/Hydrocephalus/Vomiting	NR	nd
18	Germinoma	21/M	ICP/Parinaud syndrome/Diplopy for unilateral abducens nerve palsy	NR	nd
19	Germinoma	31/M	ICP/Parinaud syndrome	NR	NR
20	Germinoma	16/M	ICP/Vomiting/Vertigo/Ataxia	nd	NR
21	Germinoma	21/M	ICP/Parinaud syndrome	NR	NR
22	Germinoma	15/M	ICP/Parinaud syndrome	nd	NR
23	Embryonal carcinoma	14/M	ICP/Vomiting/Vertigo/Ataxia	NR	nd
24	Mixed germ cell tumor	16/M	ICP/Hydrocephalus/Vomiting	NR	nd
25	Immature teratoma	25/F	ICP/Parinaud syndrome	nd	NR
26	Meningioma	72/F	ICP/Headache/Vomiting	NR	NR
27	Meningioma	44/F	Hydrocephalus/Headache	R	R
28	Meningioma	56/M	ICP/Parinaud syndrome	nd	R
29	Meningioma	36/F	Vomiting/Vertigo/Ataxia	R	R
30	Tectal plate glioma	13/F	ICP/Hydrocephalus/Vertigo	R	nd
31	Tectal plate glioma	8/F	ICP/Hydrocephalus/Headache	R	nd
32	Tectal plate glioma	16/F	ICP/Parinaud syndrome	R	NR
33	Tectal plate glioma	31/M	ICP/Headache/Diminished visual acuity	R	nd
34	Tectal plate glioma	26/F	ICP/Diplopy for unilateral abducens nerve palsy	R	R

Abbreviations: MLT, melatonin; Pre, preoperative; Post, postoperative; R, rhythmic; NR, not rhythmic; nd, not done; ICP, intracranial pressure; PPTID, pineal parenchymal tumor with intermediate differentiation; PTPR, papillary tumor of the pineal region

analyzed are shown in Fig. 1. One patient (case 1) presented with a cyst composed of a gliotic layer with a large number of Rosenthal fibres and residual pineal parenchyma (Fig. 1a), which showed intense staining for neurofilaments (NF) and synaptophysin (SYN) (Fig. 1b). Two patients (cases 2 and 3) presented typical pineocytomas with tumoral cells forming large fibrillary pineocytomatous rosettes (Fig. 1c) intensely stained for SYN and NF (Fig. 1d). The two other pineocytomas (cases 4 and 5) were pleomorphic variants with gangliocytic differentiation (Fig. 1e); the tumoral cells expressed NF with intense staining of pleomorphic cells (Fig. 1f). The fifth PPT (case 6) was a patient with a tumor of intermediate differentiation (PPTID, grade III), with neoplastic cells showing diffuse proliferation (Fig. 1g), rare mitoses, diffuse immunolabelling for neuron-specific enolase (NSE) and SYN, and only sparse tumoral cells labelled for NF (Fig. 1h). Cases 7 and 8 were patients with papillary tumor of the pineal region (PTPR), a tumoral identity in the pineal region recently described [11] and recognized by the WHO

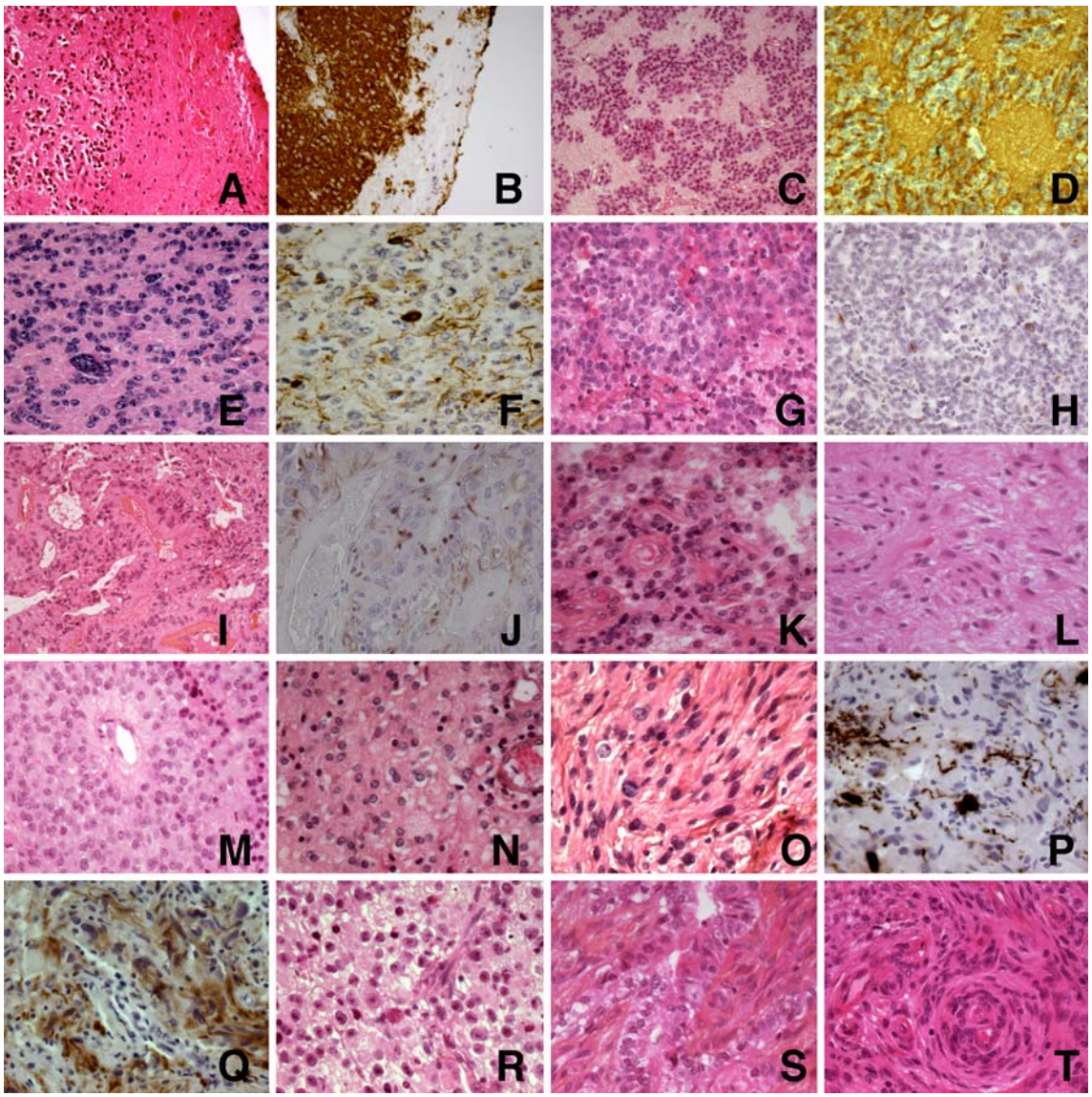


Fig. 1 Light microscopy (hemalin–phloxine–saffron (HPS) staining) and immunohistochemical features in TPR: **a**, **b** Pineal cyst with a gliotic layer and residual pineal parenchyma (**a**) and synaptophysin immunolabeling of pinealocytes (**b**). **c**, **d** Typical pineocytoma with large fibrillary pineocytomatous rosettes (**c**) and intense neurofilament immunolabeling of the pineocytomatous rosettes (**d**). **e**, **f** Pleomorphic pineocytoma with ganglionocytic differentiation (**e**) and with strong neurofilament immunoreactivity of pleomorphic cells (**f**). **g**, **h** Pineal parenchymal tumor with intermediate differentiation showing diffuse cell proliferation (**g**) and slight neurofilament immunoreactivity of tumoral cells (**h**). **i**, **j** Papillary tumor of the pineal region with papillary features (**i**) and with expression of cytokeratin in tumoral cells (**j**). **k** Oligodendroglioma with a typical honeycomb pattern. **l** Pilocytic astrocytoma with a biphasic pattern of areas with compacted bipolar cells containing Rosenthal fibers and areas with loose-textured multipolar cells. **m** Ependymoma with perivascular pseudorosettes. **n** Astrocytoma with well differentiated neoplastic astrocytes. **o**, **p**, **q** Ganglioglioma with dysplastic neurons and neoplastic glial cells (**o**), neurofilament immunoreactivity of dysplastic neurons (**p**), and GFAP immunoreactivity of glial cells (**q**). **r** Germinoma composed of large clear tumor cells with tumoral infiltration by lymphocytes. **s** Mixed germ cell tumor with germinoma and teratoma areas with glandular elements. **t** Transitional meningioma showing the coexistence of meningothelial and fibrous patterns with multiple whorls

[12]. These tumors showed diffuse proliferation with large areas with papillary features and were characterized by an epithelial-like growth pattern in which the vessels were covered by layers of columnar or cuboidal cells (Fig. 1i) and the tumoral cells expressed cytokeratin (Fig. 1j). Cases 9 to 14 were patients with gliomas. One patient (case 9) presented with oligodendroglioma grade III, composed of monomorphic cells with uniform round nuclei and a typical honeycomb pattern with significant mitotic activity and prominent microvascular proliferation (Fig. 1k). Microcalcifications were present within the tumor tissue and glial fibrillary acidic protein (GFAP) was very weakly expressed in tumoral cells and strongly expressed in intermingled reactive astrocytes. Cases 10 and 11 were patients with

pilocytic astrocytomas. The tumors presented with a biphasic pattern, with areas with compacted bipolar cells containing Rosenthal fibres and others with loose-textured multipolar cells (Fig. 1l). Case 12 was an ependymoma grade III with high cellular proliferation and perivascular pseudorosettes (Fig. 1m). The astrocytoma grade II (case 13) was composed of well-differentiated neoplastic astrocytes (Fig. 1n). Case 14 was a patient with a ganglioglioma (Fig. 1o), composed of dysplastic neurons and neoplastic glia cells, both of low malignancy. Immunoreactivity for NF (Fig. 1p) and GFAP (Fig. 1q) demonstrated the double origin of the constitutive cells. Cases 15 to 25 were patients with GCT. The germinomas were composed of large clear tumor cells with an abundant clear cytoplasm with tumoral infiltration by lymphocytes (Fig. 1r).

The mixed germ cell tumor corresponded to a germinal neoplasm exhibiting an area of teratoma with glandular elements (Fig. 1s). Four patients (cases 26–29) presented with a meningioma. The histological features of case 27 were transitional, with the coexistence of meningothelial and fibrous patterns with multiple whorls (Fig. 1t).

Melatonin rhythm

In the 29 patients with TPR, 13 out of the 24 cases investigated showed increased plasma melatonin levels at night and 11 did not. In the patient with a pineal cyst (case 1), a slight increase in plasma melatonin levels was observed before surgery at 7.00 (Fig. 2a-1) and a day/night variation in urinary melatonin levels was also observed (day 24.2 ng/12 h versus night 68.4 ng/12 h). After surgical removal of the cyst, plasma melatonin levels were low throughout the 24 h (Fig. 2a-2).

In patients presenting with PPT, a nycthemeral variation in plasma melatonin levels was observed in three out of the four patients with pineocytoma before surgery. The patient without melatonin rhythm (case 2) was the oldest pineocytoma patient. In the patient with PPTID (case 6), the 24 h melatonin profile was low, with no nocturnal increase, before surgery (Fig. 2b-1). After tumor resection, very low or undetectable melatonin levels were observed in the two patients with pineocytoma studied (Fig 2b-2).

In one patient with PTPR (case 7), a melatonin rhythm of small amplitude was observed before surgery (Fig. 2c-1). In the second patient (case 8), no melatonin rhythm was seen after surgery (Fig. 2c-2). In this case, histopathological examination of the pineal parenchyma near the tumor indicated that the pineal gland had been removed, at least partially, at the time of operation.

All six patients with glioma showed a melatonin rhythm of variable amplitude before surgery (Fig. 2c-1). After tumor resection, the two patients in whom melatonin secretion was analyzed over 24 h showed very low levels (Fig. 2c-2).

Fig. 2 Plasma melatonin levels before and/or after surgery in eighteen patients with TPR and five patients with tectal plate gliomas ▶

Melatonin rhythm was studied before surgery in eight out of eleven patients presenting with GCT; all had very low melatonin levels with no nocturnal increase. After surgery, five of the eleven, including two studied before surgery, were evaluated and showed no melatonin rhythm (data not shown).

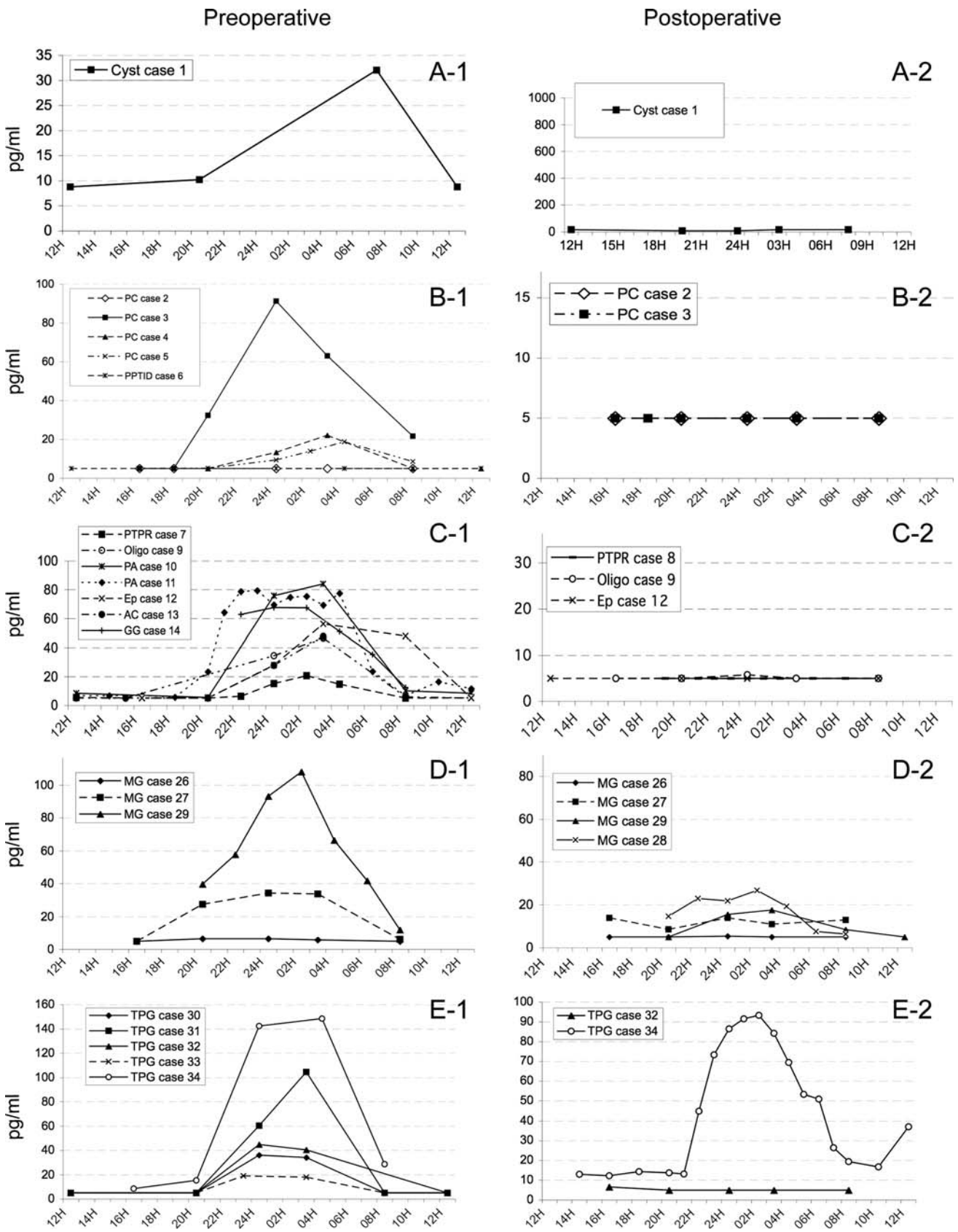
Preoperative plasma melatonin levels in three patients presenting with meningioma (Fig. 2d-1) showed a day/night variation in two cases (cases 27 and 29) and constant low levels over the 24 h in the other (case 26). This case also displayed low melatonin levels and no day/night variation after surgery. Among the patients with meningioma, case 27 presented no day/night variation in melatonin levels after surgery, while cases 28 and 29 displayed slight day/night variation (Fig. 2d-2).

Before surgery, in the five patients presenting with TPG, the plasma melatonin profile displayed a classical nocturnal increase, with nocturnal melatonin levels ranging from 19 to 148 pg/ml (Fig. 2e-1). After resection of the glioma, only one (case 34) of the two patients studied showed a nocturnal melatonin increase (Fig. 2e-2).

Discussion

TPR display similar brain imaging and clinical symptoms, irrespective of histological type [13]. Consequently, it could be of interest to establish a correlation between a specific alteration of preoperative melatonin rhythm and the histological type of TPR. It is essential, however, to have a precise diagnosis, because TPRs are histologically heterogeneous. All tumors were identified after surgery, thus providing reliable grading according to the WHO classification.

In the control group, which included patients with TPG undergoing the same surgical approach, melatonin levels before surgery showed a nycthemeral variation with high levels at night, but of variable amplitude, as observed in normal subjects [14, 15]. As melatonin levels during the night cover a very wide range, caution is needed in reporting a night-time plasma melatonin result as abnormal. Moreover, the circadian amplitude decreases with age [16] and there is also gender-dependent variation. Because our patients presenting with a TPG were young, the difference in the amplitude of the melatonin peak could be explained by inter-individual variation. Of the two patients with TPG investigated after surgery, one showed a melatonin rhythm and the other did not. The latter patient had a large tumor of about 40 mm and the surgery might have damaged the pineal parenchyma or the innervation to the pineal gland.


Preoperative
Postoperative
A-1
Cyst case 1
pg/ml
A-2
Cyst case 1
B-1
PC case 2
PC case 3
PC case 4
PC case 5
PPTID case 6
B-2
PC case 2
PC case 3
C-1
PTPR case 7
Oligo case 9
PA case 10
PA case 11
Ep case 12
AC case 13
GG case 14
C-2
PTPR case 8
Oligo case 9
Ep case 12
D-1
MG case 26
MG case 27
MG case 29
D-2
MG case 26
MG case 27
MG case 29
MG case 28
E-1
TPG case 30
TPG case 31
TPG case 32
TPG case 33
TPG case 34
E-2
TPG case 32
TPG case 34

High daytime melatonin levels have been reported in patients with TPR in some papers [3, 4, 6, 17], but were not observed in our study, in agreement with Vorkapic's report [9]. Patients with cyst or PPT might be able to synthesize melatonin, because pineal enzymes involved in the melatonin pathway, for example tryptophan hydroxylase, arylalkylamine *N*-acetyltransferase and hydroxyindol-*O*-methyltransferase, are present [4, 18, 19]. In the patient with a pineal cyst, despite the possibility of compression of the pineal parenchyma, slight day/night variation in plasma and urinary levels of melatonin was observed, suggesting that this parenchyma could secrete melatonin. In the patients with PPT, only the oldest did not show a 24 h plasma melatonin variation before surgery. In the three other PPTs, typical or pleomorphic pineocytomas, hormone production and secretion were maintained, either because there was residual normal pineal parenchyma or the tumoral tissue could still synthesize melatonin. Our results are in agreement with previous reports showing the presence of a normal circadian pattern of melatonin secretion in patients with pineocytoma [7, 9]. No melatonin rhythm was observed in the patient presenting with PPTID, a tumor with a lower degree of differentiation. Our results suggest that the 24 h melatonin rhythm was preserved in the most differentiated TPPs. PTPR is a tumor first described in 2003 [11] and now recognized by the WHO as a new tumoral entity [12], with about 50 cases described in the literature [20, 21]. The presence of increased nocturnal melatonin levels in the patient presenting with PTPR is not surprising. Indeed, this neoplasm could originate from modified cells of the subcommisural organ located beneath the pineal gland [11].

As previously shown in GCTs [7, 9, 22], all patients in our study presenting with this type of tumor, whatever the histological subtype, displayed low melatonin levels throughout the 24 h period. The low melatonin secretion in these neoplasms may result from complete destruction of the pineal gland by the tumor.

In all tumors of glial origin in the pineal region, the presence of 24 h melatonin variations is in agreement with normal function of the pineal parenchyma in these tumors, which are derived from non-pineocytomatous cells. Furthermore, a melatonin rhythm has also been reported in patients with a pilocytic astrocytoma [7, 9].

Meningiomas are relatively common in adults, but are rare in the pineal region. Surgery is the only management modality, as these tumors are benign and encapsulated [23, 24]. The absence of a day/night plasma melatonin variation has been reported in one case of meningioma of the pineal region [9], whereas another study reported the presence of this rhythm in a younger patient presenting with a meningioma [7]. In our study, the melatonin rhythm was maintained in three patients with meningioma but was absent in the oldest patient.

In agreement with previous studies [7, 9, 22, 25, 26], melatonin secretion was abolished after surgery in patients with a pineal cyst, PPT, PTPR, glial tumor, or GCT, with melatonin concentrations being either undetectable or at the limit of detection. The pineal tissue was either infiltrated by the tumor or removed at surgery with the tumor, as for the PTPR (case 8) in which normal pineal tissue was observed in the vicinity of the tumor in neuropathological preparations. The absence of a melatonin rhythm in two patients presenting with infiltrating glial tumors could be explained by the high grade of the tumor in these subjects and tumor resection could have damaged the residual pineal tissue.

In conclusion, we reported the largest series of patients with both histologically well-defined pineal tumor and 24 h melatonin profile determination before and/or after surgery. A remaining melatonin nycthemeral rhythm was observed in different types of neoplasm in the pineal region, even in tumors arising from pinealocytes. Undifferentiated or invasive pineal tumors displayed a dramatically decreased melatonin rhythm before surgery. The absence of rhythm in all germ cell tumors of the pineal region could help in the diagnosis of this type of tumor. Finally, sequential determination of melatonin profiles remains of interest. Before surgery, it enables evaluation of the functional capacity of the pineal gland in the presence of tumor tissue. The evidence for melatonin deficiency after surgery could be the pathophysiological justification for melatonin administration, in order to prevent the sleep wake-cycle disorders observed after surgery as previously described [27] and the potential post-pinealectomy syndrome reported in pinealectomized patients [28].

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