Am J Transl Res 2021;13(6):5758-5766
www.ajtr.org /ISSN:1943-8141/AJTR0127844

Review Article

Pineal region tumors: pathophysiological mechanisms of presenting symptoms

Ioannis N Mavridis[1], Efstratios-Stylianos Pyrgelis[1,2], Eleni Agapiou[1,3], Maria Meliou[1,4]

[1]"C.N.S. Alliance" Research Group, Athens, Greece; [2]1st Department of Neurology, "Eginition" Hospital, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; [3]Department of Physical Medicine and Rehabilitation, "Asklipeion Voulas" General Hospital, Voula, Athens, Greece; [4]Infectious Diseases Unit, 3rd Department of Internal Medicine, "Hellenic Red Cross" General Hospital of Athens, Athens, Greece

Received December 8, 2020; Accepted May 6, 2021; Epub June 15, 2021; Published June 30, 2021

Abstract: Pineal region tumors (PRTs) affect all ages, with a remarkable proportion of cases occurring in children. They are mainly classified into three categories, namely germ cell tumors (GCTs), pineal parenchymal tumors (PPTs), and other tumors such as gliomas and tumors of the surrounding structures. The purpose of this article is to review the current literature regarding pathophysiological mechanisms of the presenting clinical features of patients with PRT. The usual presentation of PRTs is the symptoms of obstructive hydrocephalus and intracranial hypertension, such as headache and vomiting. However, there is a remarkable spectrum of clinical findings that can be caused by such lesions. These include ophthalmologic and endocrinologic disturbances, motor and sensory abnormalities, and cognitive and psychiatric symptoms. The unique anatomic location of the pineal gland, which is close to many vital brain structures, is crucial for the explanation of most of those findings. In rare cases, manifestations of intracranial bleeding may be the presenting feature of a PRT. Tumor histology and patient's age can affect the clinical presentation. Hydrocephalus is the most common clinical syndrome of a PRT because of the location of the pineal gland. Presenting symptoms also include ophthalmologic, endocrinologic, motor, sensory, cognitive, and psychiatric symptoms. Clinicians should be aware of the initial symptoms of PRTs, including the misleading ones, in order to avoid delay in the diagnosis and management of these life-threatening lesions.

Keywords: Germ cell tumors, obstructive hydrocephalus, pineal gland, pineal parenchymal tumors, pineal region tumors

Introduction

Pineal region tumors (PRTs) constitute 0.4-1% of all central nervous system (CNS) tumors in adults and 3-8% of CNS tumors in children [1-3]. A higher incidence (up to 3.2%) has been reported in Japanese population [3]. Median age at presentation is 12-13 years [4, 5]. PRTs are more frequent in children and there is a slight male predominance (2:1 male to female ratio) [4, 6, 7].

PRTs are a heterogeneous group of lesions [7] with a significant proportion consisting of mixed cell types [8]. According to the World Health Organization (WHO), PRTs are classified into three categories: 1) germ cell tumors (GCTs) (including germinomas and non-germinomatous GCT) [9], 2) pineal parenchymal tumors (PPTs) (including pineocytomas, pineoblastomas, and PPTs of intermediate differentiation) [1, 3, 8, 10], and 3) other tumors such as astrocytomas, ependymomas, mixed gliomas, and even more uncommon tumors of the surrounding structures [2] (e.g., meningiomas, dermoids, epidermoids [11-13], rhabdomyosarcomas [14], histocytic sarcomas [2], and primary pineal melanomas [15]). Pineal region metastases can also occur [16, 17]. The majority of these tumors are GCTs followed by other types, namely pineoblastomas, pineocytomas, astrocytomas, and ependymomas [5]. Histopathological diagnosis may be unsuccessful in up to 20% of cases [8].

Early diagnosis of brain tumors is of paramount importance. Given that this usually follows the first clinical manifestations of the tumor, clini-

cians need to be aware of the first warning symptoms and signs of those patients. Thus the purpose of this article was to review the current literature regarding the presenting clinical features of patients with PRT, as well as their underlying pathophysiological mechanisms.

Symptoms of obstructive hydrocephalus and intracranial hypertension

Almost all PRT patients have hydrocephalus by the time of presentation [9]. Obstructive (triventricular, non-communicating) hydrocephalus, due to obstruction of the Sylvian aqueduct by the tumor, is the main underlying mechanism of the presenting symptoms in these patients [3, 14, 17-21]. Obstruction due to compression or neoplastic infiltration can be acute, subacute [17], or late (chronic) [22]. The commonest (approximately 90%) [23] presenting symptoms of pineal space-occupying lesions are therefore those of raised intracranial pressure (ICP), presenting as mainly new and/or severe headache [1-3, 6, 8, 9, 13, 14, 24-30], occasionally chronic and/or unilaterally located, which improves at rest [21]. Headache has been reported in up to 100% of patients with pineal meningiomas [28].

Other symptoms of intracranial hypertension include nausea and vomiting, while papilledema is a common presenting sign [1, 2, 8, 9, 14, 20, 21, 27, 28, 31-36]. Children usually present with symptoms of raised ICP of short duration [2, 18, 27] with vomiting often being more common than headache, as for example in children with pineoblastoma, where the frequency of these two symptoms is 65% and 47% respectively [1]. Abnormal increase in head circumference may be noticed in infants [9].

Other concomitant hydrocephalic symptoms include cognitive deterioration, gait disturbance, imbalance and/or ataxia, and urinary incontinence [15, 17, 26, 28, 37]. These symptoms may quickly [15] or even suddenly [27] progress to photophobia [15] and mental status decline [27]. Deterioration of consciousness is usually the next step and varies from disturbed consciousness [28, 38, 39] to lethargy [9, 15] and even coma [18]. Remarkably, pineal cysts may unusually present with transient episodes of depressed consciousness (syncope-like) [34]. Finally, PRT causing hydrocephalus may initially be cryptogenic with the lesion being revealed on subsequent imaging studies [18].

Ophthalmologic symptoms

Ophthalmologic manifestations are not as common, but they are more characteristic of pineal space-occupying lesions than those of raised ICP. Parinaud's syndrome, characterized by upward gaze paresis and caused by pressure of the dorsal midbrain, has been described in many cases [1, 3, 6, 7, 9, 13, 20, 28, 29, 31-33, 37, 38, 40, 41]. This abnormality is however uncommon among patients with pineal meningiomas [28]. Other clinical features include diplopia [1-3, 7, 25, 33, 37, 38, 41], often due to abducens nerve paresis [2], unilateral partial oculomotor nerve palsy [33], discoordinative eye movements, pupillary dilatation, paralysis of adduction during convergence, nystagmus [19], retrobulbic pressure [3], decreased visual acuity [35], and other visual disturbances [13, 24, 29, 30, 33, 34, 36, 42-45]. Visual field defects and oculomotor abnormalities are among the principal presenting findings in children with pinealomas and germinomas [4]. Visual disturbances can rarely be the result of coexistent retinal tumor in children with trilateral retinoblastoma (bilateral retinal tumors simultaneously with a pineal tumor) [46, 47].

Pineal tumors may occasionally present with a paraneoplastic ophthalmologic syndrome prior to evident appearance of symptoms related to primary tumor's growth. Such paraneoplastic syndromes can cause rapid loss of vision and autoimmune reaction, causing inflammatory ocular symptoms such as uveoretinitis [19], and even features of ocular myasthenia [48].

Endocrinologic symptoms

Endocrinologic symptoms in PRT patients appear quite frequently. Hypothalamic and/or pituitary dysfunction, which may occur due to compression, invasion or surgical damage to the hypothalamus, pituitary gland, and pituitary stalk, is usually the underlying cause [47, 49-51]. The hypothalamus can be specifically affected by pineal lesions due to their space occupying properties, loss of inhibitory influences, or even metastasis/extension of the tumor [52]. Manifestations include diabetes

insipidus [7, 19, 36, 47, 51-54] characterized by polyuria and polydipsia [7, 30, 51-53], disorders of puberty [6, 53] such as precocious puberty [55, 56], symptoms of panhypopituitarism [47, 54], or isolated dysfunction of the anterior pituitary gland [54], hypogonadotropic hypogonadism, and adrenal insufficiency [57]. Precocious puberty observed in boys with choriocarcinomas or germinomas with syncytiotrophoblastic cells is due to the luteinizing hormone-like effect of β-human chorionic gonadotropin secreted in the CSF [9]. The clinical manifestations of PRT-related endocrinologic disturbances may also include fatigue, gynecomastia, anorexia, and low libido [30].

Cognitive symptoms

Cognitive symptoms in patients with PRT are infrequent [29] and usually attributed to obstructive hydrocephalus [18, 39]. Cognitive deterioration may be progressive [17] and prolonged for months [26], and can even manifest as memory disturbance [9, 29]. Patients with pineal germinoma rarely present with amnesia [31]. Such memory disturbances, which may impair recent and antegrade episodic memory, involve both verbal and visual memory modalities, and progress over months, can be attributed to tumor extension to the perisplenial region and fornix [31].

Motor/sensory symptoms

Hemiparesis and ataxia are among the less commonly reported PRT symptoms [6, 24, 26, 28]. Large pineal cysts may rarely present with corticospinal and corticopontine fibers' deficits including hemiparesis, hemisensory loss, ataxia, and other sensory deficits [32, 33, 58], such as paresthesias [34]. Weak or unsteady gait has been reported in about 1/3 of the affected children [1]. Gait imbalance [3, 6, 15, 26, 28] may progressively lead to inability to walk [17]. Interestingly, secondary Parkinsonism may be observed in PRT patients due to the involvement of the nigro-striatal-pallidal system, mass effect to the thalamus, massive hydrocephalus, or damage to dopamine receptors [29]. Clinical findings include bradykinesia, broad-based gait [29], limb rigidity [1, 59], and resting tremor [59].

Psychiatric symptoms

The pineal gland is considered to be involved in psychiatric disorders, although the underlying mechanism is not clearly understood. Disruption of melatonin synthesis, or its secretion, may contribute to the development of such symptoms [11]. Manifestations include psychotic symptoms such as schizophrenia, anxiety, depression, and behavioral abnormalities (e.g. compulsions) [11]. Motivation can be severely affected as well [31]. Emotional disturbances may rarely be a presenting feature of benign glial cysts of the pineal gland [32], while extensive PRTs affecting the hypothalamus can even lead to anorexia nervosa [42, 57, 60]. So, organic disorder should be excluded before a psychiatric diagnosis is set, particularly in cases of atypical PRT presentation [11, 42].

Other symptoms

PRTs may rarely cause hemorrhage [38, 61, 62] and present with symptoms of intratumoral hemorrhage [62-64], subarachnoid hemorrhage [65], intraventricular hemorrhage [56], or pineal apoplexy [38]. Rare symptoms of PRTs include normal pressure hydrocephalus (gradual cognitive impairment, walking difficulty, urinary incontinence) [16, 66], cerebellar deficits [32], fever [1, 42], clinical hypernatremia [42, 57], inability to speak (in children) [1], slow speech [29], poor handwriting [29], seizures [9, 33], and tinnitus [29]. It should be also noted that drop metastases from CSF seeding (especially with GCTs, PPTs, and ependymomas) can produce radiculopathy and/or myelopathy [9].

Finally, in a few reports PRTs were accidentally diagnosed due to presenting symptoms of coexisting pathologies. Such cases include chronic rhinorrhea due to concomitant frontal encephalocele (along with pineal epidermoid cyst) [12], sudden unilateral deafness accompanied by tinnitus and vertigo due to acoustic neuroma (simultaneously with pineoblastoma) [67], and diabetes insipidus resulting from a suprasellar mass (germinoma) [68]. As previously mentioned, pineal and suprasellar GCTs may coexist (bifocal germinomas) [54, 69, 70]. **Table 1** summarizes the reported underlying pathophysiological mechanisms of the PRTs' presenting symptoms.

Clinicopathological data

A great variety of different types of tumors can affect the pineal region as summarized in

Table 1. The reported underlying mechanisms of the PRTs' presenting symptoms

► Obstructive hydrocephalus/intracranial hypertension
► Paraneoplastic syndrome/autoimmune reaction
► Hypothalamic dysfunction
► Pituitary dysfunction
► Compression/edema of the corticospinal and corticopontine fibers
► Compression/edema of the nigro-striatal-pallidal system
► Mass effect to the thalamus
► Damage to dopamine receptors
► Disruption of melatonin synthesis or its secretion
► Intratumoral hemorrhage
► Subarachnoid hemorrhage
► Intraventricular hemorrhage
► Pineal apoplexy
► Drop metastases from CSF
► Compression/edema of the cerebellum
► Hypernatremia
► Coexisting tumor

CSF, cerebrospinal fluid; PRTs, pineal region tumors.

Figure 1. **Figure 2** shows reported frequencies of different PRTs' categories. GCTs comprise 1-3% of intracranial neoplasms [6, 7] and most frequently arise in the pineal and suprasellar region [7, 70]. The peak incidence of intracranial GCTs is during the 2nd decade of life [6, 7] with a median age of 10-12 years at diagnosis [7]. The prognosis for GCT and benign tumors is favorable, with potentially achievable 100% control [74].

PPTs arise from pineocytes or their precursors, and include pineocytomas (45%), pineoblastomas (45%) [1, 8], and the least frequent PPTs of intermediate differentiation (10%) [3, 10] (**Figure 1**). Patient age range is between 10-65 years for pineocytomas (most frequent between 25-35 years) [3] and 24-60 years for PPT of intermediate differentiation [10]. Pineoblastoma occurs primarily in children with a median age of 4 years at diagnosis [1]. PPTs and astrocytomas fare prognostically less well than GCTs [74].

Symptoms of pineal meningiomas usually develop insidiously and their average duration is 9-25 months [28]. Papillary tumor of the pineal region is a recently recognized rare entity that usually presents as a solitary mass with or without hydrocephalus [35, 40, 72]. Trilateral retinoblastoma is an interesting rare combination of unilateral or bilateral retinoblastoma with a midline intracranial neoplasm usually in the pineal or suprasellar region [46, 47]. Furthermore, the pineal region is an unusual site of brain metastases [16, 17, 41] and most metastatic pineal lesions are asymptomatic [41]. When symptomatic, this is usually due to hydrocephalus [43, 75].

Pineal cysts [11-13, 62] are common intracranial findings [33, 62] on imaging (1.5-4.3% of brain magnetic resonance images) and autopsy studies (25-41%). They are usually asymptomatic until they reach a size of ≥ 2 cm [62]. Large symptomatic pineal cysts are rare [33]. Mean age at presentation is 29 years (range: 15-46 years) and male to female ratio is 1:3 [33]. They have the same presenting symptoms as PRTs [34] and hemorrhage in asymptomatic pineal cysts can cause sudden onset of symptoms [38]. Patients with pineal cysts who are on antiplatelet medication are at greater risk of pineal hemorrhage [38]. It is noteworthy that Wisoff and Epstein have described three clinical syndromes associated with pineal region cysts: 1) paroxysmal headache with gaze paresis; 2) chronic headache, gaze paresis, papilledema, and hydrocephalus; and 3) pineal apoplexy with acute hydrocephalus [62].

Discussion

Although the usual presentation of PRTs is hydrocephalic symptoms, there is a remarkable spectrum of clinical findings that can be caused by such lesions via several different mechanisms. These include ophthalmologic and endocrinologic disturbances, motor and sensory abnormalities, and cognitive and psychiatric symptoms. The unique anatomic location of the pineal gland, which is close to many vital brain structures, is crucial for the explanation of the majority of those findings. In rare cases, manifestations of intracranial hemorrhage may be the presenting feature of a PRT. Tumor histology does matter, as different syndromes are commoner with different pathologies. Finally, it is important to remember that age matters as

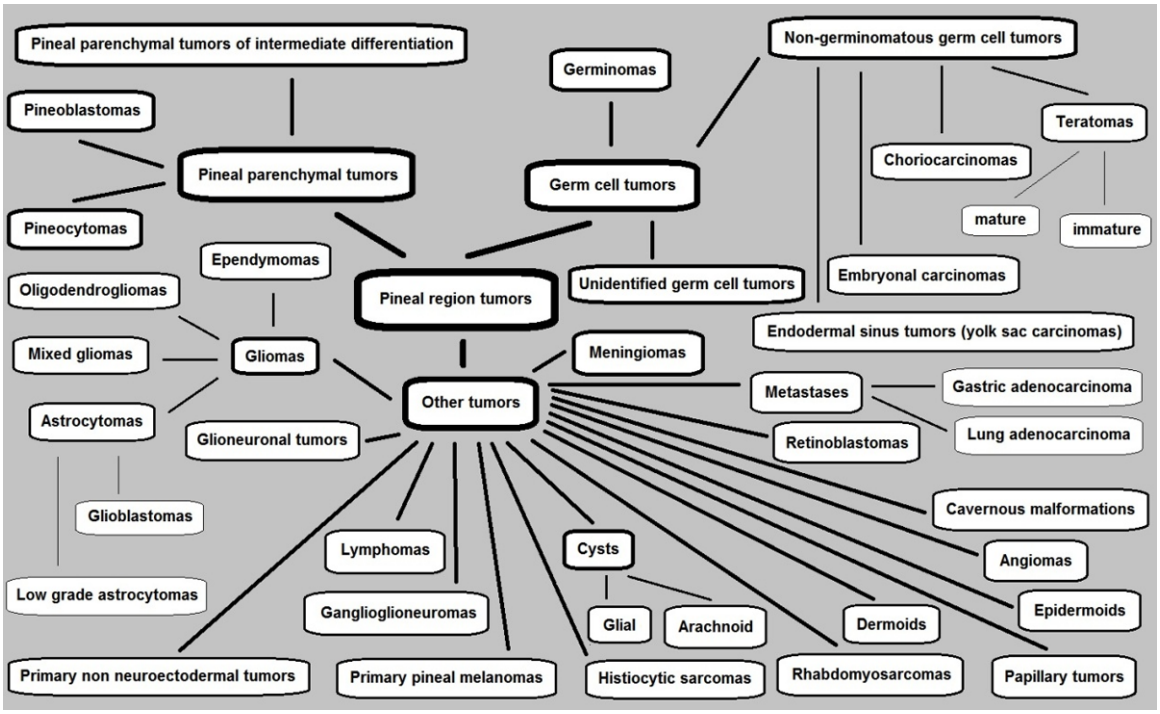

Figure 1. Summary of the tumors and other space-occupying lesions of the pineal region [1-3, 5, 8-15, 17, 35, 40, 46, 47, 59, 71-73].

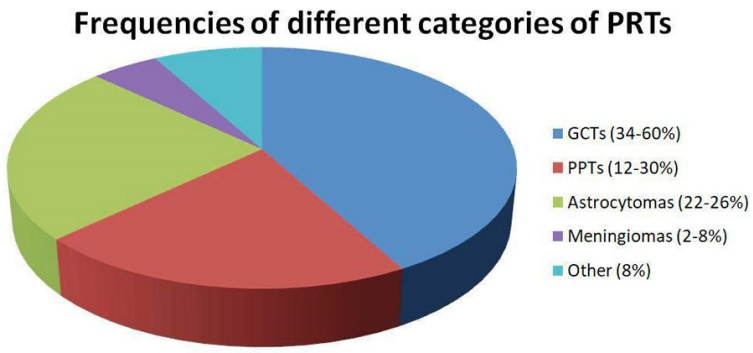

Figure 2. Reported frequencies of different categories of PRTs [3, 9, 23, 28] (PRTs, pineal region tumors; GCTs, germ cell tumors; PPTs, pineal parenchymal tumors).

well, as PRT is a clinical condition that affects pediatric population in a major proportion of cases.

Conclusion

PRTs are rare brain tumors that affect children as well as adults. Hydrocephalus is the commonest presenting clinical syndrome because of the particular location of the pineal gland, and intracranial hypertension is the most frequent underlying mechanism. The clinical spectrum of presenting symptoms extends, however, to include ophthalmologic, endocrinologic, motor, sensory, cognitive, psychiatric, and other symptoms. Tumor histology and patient's age can affect the clinical manifestations. Clinicians need to be aware of the initial symptoms of PRTs, including the misleading ones, in order to avoid delay in the diagnosis and management of these life-threatening lesions.

Disclosure of conflict of interest

None.

Abbreviations

CNS, central nervous system; CSF, cerebrospinal fluid; GCT, germ cell tumor; ICP, intracranial pressure; PPT, pineal parenchymal tumor; PRT, pineal region tumor; WHO, World Health Organization.

Address correspondence to: Dr. Ioannis N Mavridis, "C.N.S. Alliance" Research Group, Athens, Greece. E-mail: pap-van@otenet.gr

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