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Original article

Paraneoplastic neurological disorders in children with benign ovarian tumors

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Abstract

Aim: Paraneoplastic neurological diseases (PND) are rare, but potentially treatable disorders. Paraneoplastic encephalitis is rapidly emerging as an important but likely under-recognized condition in children. The aim of this study was to assess the prevalence and spectrum of PND in children with benign ovary tumor and the long-term outcome. *Patients and methods:* We retrospectively reviewed the charts of all female patients below 18 years of age diagnosed with a benign ovarian tumor proven by pathology between January 1993 and December 2010. All the clinical symptoms developed within 5 years of tumor diagnosis and the related investigations were recorded. *Results:* There were total 133 children and adolescents with benign ovarian tumors, mostly mature teratoma. Six patients (4.5%) had neuropsychiatric manifestations and all but one were beyond age 10 years. The most common neuropsychiatric presentations were depression or low mood (84%), headache (50%), mutism (50%), hypoventilation (50%), seizures (30%), hallucination (30%), vomiting and hypersalivation (30%). Three patients (2.2%) had serious PND including acute disseminated encephalomyelitis in 1 and anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis in 2. Although all of three improved after tumor removal, one without immunotherapy had neurological sequelae and prolonged ICU stay. *Conclusion:* The prevalence of PND in benign ovary tumor is not so uncommon in children. It is important to survey ovary tumors in female adolescents with subacute presentation of multiple-level involvement of neuraxis where no clear alternate diagnosis is possible. Treatment of serious PND associated with ovary tumors should include immunotherapy in addition to tumor removal.

Keywords: Paraneoplastic neurological disorders; Paraneoplastic encephalitis; Children; Benign ovarian tumors; Ovarian teratoma

1. Introduction

Paraneoplastic neurological disorders (PND) are rare, but potentially treatable disorders. These disorders are associated with tumor, but are not caused by the direct tumor invasion, metastasis or consequences of treatment [1]. PND can present with multiple clinical manifestations like encephalitis, autonomic failure, peripheral neuropathy, cerebellar ataxia, visual complains and many others [2]. PND are most commonly recognized in adults with cancer and the prevalence varies from cancer to cancer. PND can occur in 2–3% of the patients with neuroblastoma or small cell lung carcinoma and in 30–50% of the patients with thymoma and sclerotic myeloma. Overall,

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Table 1
Paraneoplastic neurological manifestations in 6 children with benign ovarian tumors.

Patient	Type of tumor	Age at diagnosis of tumor	Time between diagnosis of tumor and onset of neurological manifestations	Neuropsychiatric manifestations	Investigations	Clinical diagnosis/ treatment	Follow up duration	Outcome
1	MT	7 yrs	-2 mos	Intractable seizure, severe SIADH, aggressive behaviors, talkative, headache, dyskinesia, mutism, hypoventilation	Brain MRI: right parietal hyperintensity lesion CSF: pleocytosis EEG: focal discharge	Anti-NMDAR encephalitis/tumor removal	1 yr	Mutism
2	MT	14 yrs	-2 mos	Hallucination, anxiety, depressed mood, seizures, severe vomiting, hypersalivation, diplopia, nystagmus, hypoventilation, legs weakness, urine retention, anorexia nervosa	CSF: pleocytosis EEG: negative Brain and spinal cord MRI: multiple gray and white matter hyperintensity	ADEM/tumor removal, IVIG, methyprednisolone	3 yrs	Remitted at 3 mos
3	MT*	14 yrs	-3 wks	Hallucination, depression, dyskinesia, hypoventilation, headache, hypersalivation, mutism	CSF: negative EEG: negative Brain MRI: negative anti-NMDAR Ab in CSF and serum: positive	Anti-NMDAR encephalitis/tumor removal, IVIG, methyprednisolone	3 yrs	Remitted at 2 mos, recurrent dyskinesia 2 yrs later, remitted 1 mo after tumor removal
4	MT	17 yrs	-1 yrs	Depression, insomnia	NA	Depression/tumor removal, antidepressant	9 yrs	Remitted at 1 yr
5	MT	10 yrs	-3 yrs	Low mood, mutism	NA	Adjustment disorder/tumor removal, psychotherapy	8 yrs	Remitted at 1 yr
6	SCA	14 yrs	-2 mos	Dizziness, low mood	NA	Adjustment disorder/tumor removal, psychotherapy	13 yrs	Remitted at 6 mos

Ab: antibodies; ADEM: acute disseminated encephalomyelitis; anti-NMDAR: anti-*N*-methyl-D-aspartate receptor; MT: mature teratoma; NA: not available; SCA: serous cystadenoma; SIADH: syndrome of inappropriate anti diuretic hormone secretion.
* Tumor relapse; + after; - before; mos: months; yrs: years.

it is estimated that 0.5–1% of all adult patients with cancer have clinically disabling PND [1,3].

Little emphasis is given to the possibility of PND in children. There have been some small case series of childhood PND. The most common childhood PND is opsoclonus myoclonus syndrome, a severe disabling neurological illness of early childhood that frequently (43%) associated with neuroblastoma [4]. Paraneoplastic limbic encephalitis, characterized by subacute onset of memory impairment, temporal lobe seizures and affective disturbances, is mainly recognized in adults with lung neoplasm [5]. There have been limited reports published in English on the cases of pediatric limbic encephalitis [6–11]. The recently described anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis, predominantly affects female children and young adults, seems to be more frequent than any other known paraneoplastic encephalitis [12]. Most patients with anti-NMDAR encephalitis develop typical cortico-subcortical encephalopathy including psychosis, memory deficits, seizures, language disintegration, abnormal movements, and breathing instability. About 59% of patients with anti-NMDAR encephalitis have ovarian tumors, mostly teratoma [12].

Although ovarian cancers are extremely uncommon in children, teratomas are the most common. Mature teratomas are benign and there have been few case reports of paraneoplastic syndromes in addition to anti-NMDAR encephalitis, including opsoclonus-myoclonus syndrome [13], polyarthritis [14], juvenile dermatomyositis [15] and autoimmune hemolytic anemia [16]. Since the list of the PND continues to increase day by day, it remains to be determined the prevalence of childhood PND associated with ovarian tumors. The aim of this study was to assess the spectrum of PND in children with benign ovary tumor and the long-term outcomes.

2. Patients and methods

This study was approved by Institutional Review Board in Kaohsiung Chang Gung Memorial Hospital. We retrospectively review the charts of all female patients below 18 years of age diagnosed with a benign ovarian tumor by pathology between January 1993 and December 2010. The clinical data including age of onset, tumor pathology, neurological manifestations, psychiatrics symptoms and laboratory data including blood test, neuroimaging studies, cerebrospinal fluid (CSF) test, and electroencephalogram (EEG) were collected. All the clinical symptoms developed within 5 years of tumor diagnosis were recorded.

3. Results

There were total 133 children and adolescents with benign ovarian tumors diagnosed during the 17 years. The mean age of tumor diagnosis was 13.2 years old (ranged 1–18 years). The most common pathology was mature teratoma (75%), cystadenoma (20%), fibroma (2%) and thecoma (1%). Eight patients (6%) have tumor recurrence. The mean duration of follow up was 4.5 years (0.1–20 years).

Six (4.5%) of the 133 children and adolescents had isolated or combined neuropsychiatric symptoms at some stage during their diseases. The main tumor types were mature teratoma (83.3%) and serous cystadenoma (16.7%). The mean age of PND onset was 12.6 years old with only one patient below 10 years of age. All patients had neuropsychiatric symptoms preceding the diagnosis of the tumor (by a median of 2 months). The most common neuropsychiatric presentations were depression or low mood (84%), headache (50%), mutism (50%), hypoventilation (50%), seizures (30%), hallucination (30%), vomiting and hypersalivation (30%). The mean duration of follow up was 8.3 years (ranged 1–13 years). Five patients' symptoms completely remitted 5 months after tumor removal (ranged 2 months–1 year) and one remained mutism (Table 1).

Three patients (Patients 1–3) had severe encephalitis-like and psychiatric symptoms and were hospitalized in ICU before the diagnosis of ovarian teratoma. All three patients had psychiatric symptoms and hypoventilation. Two patients (Patients 1 and 3) had prominent involuntary movements and orofacial dyskinesia. Patient 2 had bilateral lower leg weakness and urinary retention and was diagnosed as acute disseminated encephalomyelitis (ADEM) by MR images (Fig. 1). Patient 1 had refractory seizures and severe hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion (SIADH). Two patients had pleocytosis in their CSF. There was two patients undertook autoantibodies survey which showed high titles of anti-NMDA antibodies in their CSF. Patient 3 had relapsed oromotor dyskinesia 2 years later and subsided soon after the recurrent ovarian tumor was removed. The pathology demonstrated neuronal components in her teratoma (Fig. 2). All patients improved after tumor removal. Two patients also received immunotherapy during their hospitalization (39 days and 53 days, respectively) and both fully recovered. One patient (Patient 1) without immunotherapy stayed in ICU for 89 days and remained mutism during the 1-year follow up period.

4. Discussion

This is the largest and the longest follow-up clinical study of PND associated with benign ovarian tumors in children and adolescents. We found that 4.5% of the children with benign ovarian tumors had neuropsychiatric manifestations and most of them were beyond age 10 years. Five patients' (83%) symptoms remitted completely after tumor removal. Three patients (2.2%)

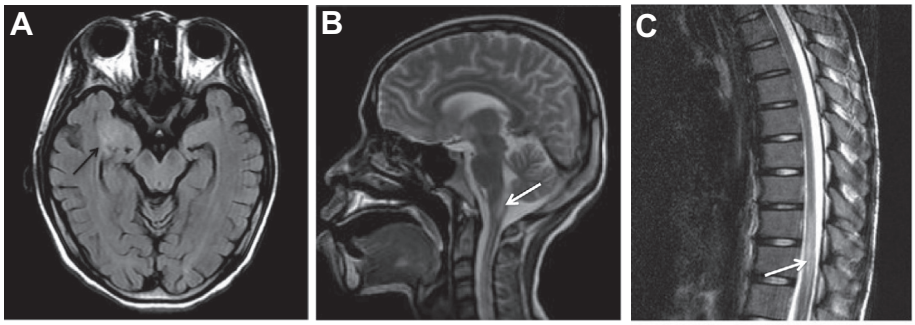

Fig. 1. Magnetic resonance imaging of patient 2 showed multiple hyperintensity (arrows) over (A) right mesial temporal area (FLAIR) (B) brain stem (T2-weighted) and (C) thoracic spinal cord (T2-weighted).

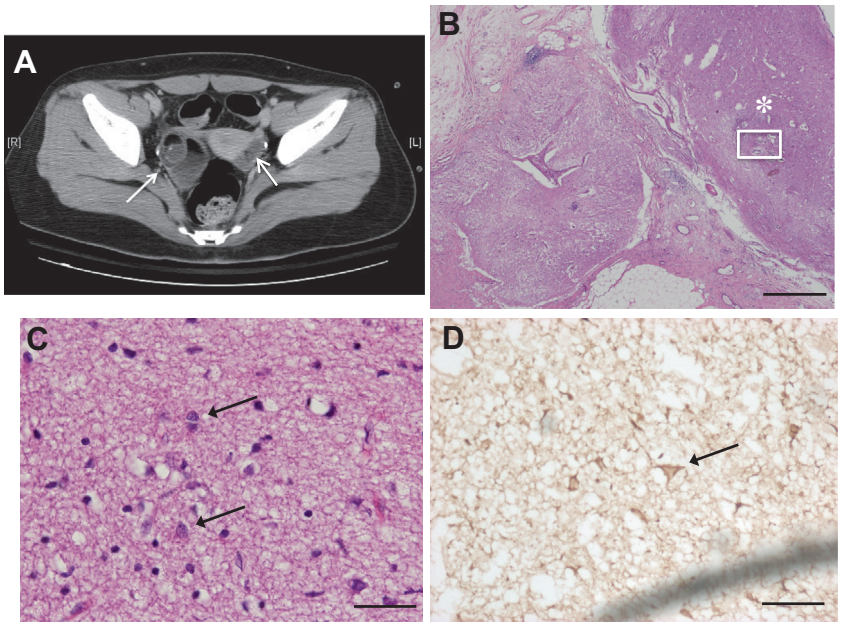

Fig. 2. (A) The pelvic computed tomography of patient 3 shows bilateral cystic ovarian lesions (white arrows). (B) The pathology of the removed ovary teratoma of the same patient demonstrated nervous tissue by HE stain (star). (C) Higher magnification of the inset showed the neuronal-like cells (black arrows) and a network of cell processes that immunolabeled with MAP (brown staining), a marker specific for neurons and dendritic processes (D). Scale bar = 250 μm in (B) and 100 μm in (C) and (D).

had serious PND including acute disseminated encephalomyelitis in 1 and anti-NMDAR encephalitis in 2. Although all three improved after tumor removal, one without immunotherapy had neurological sequelae and prolonged ICU stay.

Little attention has been given to the possibility that neurological involvement in children with neoplasms is paraneoplastic. In our cohort study, although 8 patients have local tumor recurrence, none had distal tumor metastasis or chemotherapy. Furthermore, most of the symptoms remitted or improved after tumor removal, although the effects of anesthesia cannot be denied. According to a large case study of adult patients with paraneoplatic limbic encephalitis, affective changes, personality changes, and sleep disorders were found in 14%, 6% and 14% of those patients, respectively [5]. Since we did not perform the onconeuronal antibody assessment in all those children, these neuropsychiatric manifestations are classiofied as "possible" PND [17]. Our data imply that the prevalence of PND in benign ovary tumor is not so uncommon in children.

Paraneoplastic encephalitis is rapidly emerging as an important and likely under-recognized condition among the pediatric population [18]. Two of our three patients with serious encephalitis had available CSF for antibodies studies and been proven as anti-NMDAR encephalitis. Although Patient 1 had severe SIADH and hyponatremia has been frequently occurred in patients with PND associated with VGKC (voltage-gated-potassium channels) [19], our case demonstrated that there is a wide spectrum in the clinical manifestations of childhood anti-NMDAR encephalitis. In patient 2, although

the MRI features and the neurological symptoms were suggestive of ADEM, the prominent psychiatric symptoms and hypersalivation suggested that she might also have anti-NMDAR encephalitis. In most case of anti-NMDAR encephalitis, MRI is usually normal or demonstrates nonspecific lesions in the grey matter [12]. However, there were some cases of anti-NMDAR encephalitis presenting with seronegative neuromyelitis optica, ADEM, or multifocal white matter lesions [12,20,21]. These data suggests that there might be an overlap between anti-NMDAR encephalitis and demyelinating diseases, potentially involving other immunological mechanisms.

It is of note that most of the PND occurred in children aged beyond 10 years in our study. Consistent with our observation, the incidence of benign ovarian tumor was 58%, 31%, and 15%, for the patients over 18, under 18, and under 14 years of age, respectively, in anti-NMDAR encephalitis [12]. The most common tumor is teratoma, which may be related to onconeural antigen expressed from the neuronal tissue of the teratoma [22]. Although ovarian cancers only constitute 1% of all childhood malignancies, teratomas are the most common neoplasm [15]. It is therefore important to survey ovarian tumors in female adolescents with subacute presentation of multiple-level involvement of neuraxis where no clear alternate diagnosis is possible.

Prompt identification of PND is important to make an early diagnosis of the tumor for removal. There are no evidence-based recommendations available regarding the immunosuppressive therapy for all cases with PND [1]. However, the recent studies suggest that those antibodies against neuronal surface antigens and synaptic receptors are excellent predictors of a better response to immunotherapy [23]. We also observed that although all three cases improved after tumor removal, one without immunotherapy had neurological sequelae and longest ICU stay. The other 2 patients had fully recovered after 2 courses of immunotherapy. Treatment of serious PND associated with ovarian tumors, therefore, should include surgical removal of tumor as well as immunotherapy.

Limitations of this retrospective study are that children have been investigated in various ways over the 17 years, lacking of an accepted gold standard for the systemic review of neurological symptoms. Therefore, there were no records of peripheral nervous system involvements in all the children with benign ovarian tumors. We also did not perform the paraneoplastic antibody evaluation in those children. However, it should be noted that only 60–70% will have detectable antibodies and that they can be seen in patients without PND.

Our studies demonstrated that the prevalence of PND in benign ovarian tumor is not so uncommon in children. Paraneoplastic encephalitis is rapidly emerging as an important condition among the pediatric population. Prompt identification of PND is important to make an early diagnosis of the tumor. Treatment of serious PND associated with ovary tumors should include tumor removal as well as immunotherapy.

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