Original Article

Long-term neurological outcomes of children with neuroblastoma with opsoclonus-myoclonus syndrome

Qing Sun[1], Yinhao Wang[2], Yao Xie[1], Penghui Wu[1], Shuo Li[1], Weihong Zhao[1]

[1]Department of Pediatrics, Peking University First Hospital, Beijing, China; [2]Department of Ophthalmology, Peking University Third Hospital, Beijing, China

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Correspondence to: Weihong Zhao, MD. Department of Pediatrics, Peking University First Hospital, No. 1 Xianmen Street, Xicheng District, Beijing 100034, China. Email: zhaowh3212@126.com.

Background: Neuroblastoma with opsoclonus-myoclonus syndrome (OMS-NB) is a rare disease in children. Few studies of long-term outcome of children with OMS-NB were conducted. This study aimed to review the rate of recovery of neurological symptoms and the long-term neurological outcomes of children with OMS-NB.

Methods: This study retrospectively assessed 14 children with OMS-NB diagnosed at Peking University First Hospital from May 2011 to November 2019. Demographic data, neurological symptoms, oncological status and treatments were retrospectively reviewed from the records. Neurological sequelae were recorded by clinical and remote follow-up.

Results: During the acute stage, myoclonus and ataxia were observed in all children while opsoclonus was observed in 10/14 children. The median durations of neurological symptoms were 15 months (range, 5–48 months). Approximately 93% (13/14) children revealed neurological sequelae. Significant correlations were as follows: motor retardation with female gender ($P<0.001$) and residual tumors ($P<0.05$); language impairment with non-adrenal-gland-located tumors ($P<0.05$). There were no obvious factors that had a statistical relationship with cognitive disorder or behavioral changes.

Conclusions: Children with OMS-NB have favorable outcomes in terms of neurological symptoms. Neurological sequelae occurred in almost all children. Children with different features tend to reveal different sequalae. Features of female gender and residual tumors tend to reveal motor retardation while that of non-adrenal-gland-located tumors tend to reveal language impairment.

Keywords: Neuroblastoma (NB); opsoclonus-myoclonus syndrome (OMS); neurological symptoms; neurological sequelae

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Introduction

Opsoclonus-myoclonus syndrome (OMS), also known as "dancing eyes syndrome", is a rare childhood autoimmune disease that is characterized by rapid, multidirectional and conjugate eye movements (opsoclonus), myoclonus, ataxia and behavioral changes, such as irritability and sleep problems (1). In 50% of children with OMS, a neuroblastoma (NB) is detected (2); this condition is called NB with OMS (OMS-NB), and OMS occurs in 2–3% of children with NB (3). In addition to its paraneoplastic association with NB, OMS can also be idiopathic, associated with infection (post- or para-infectious) (4), or the paraneoplastic manifestation of another adult tumor (5).

OMS is commonly thought to be associated with autoreactive T-cell activation. But B-cell activation and antigen presentation are also recognized as important

contributors to pathophysiology (6). Autoimmunity may be mediated through autoantibodies in a proportion of OMS cases (7). Besides, genetic mimics of OMS also exist although these are also exceedingly rare (8). OMS-NB is believed to be associated with cross-reactive autoimmunity between NB cells and the central nervous system (9). However, surgery for tumors, which is thought to be a way to remove the antigen physically, is insufficient in improving OMS.

OMS-NB usually has a good oncological prognosis, namely, a high survival rate and low relapse rate, since these children often have favorable prognostic features (10,11). However, approximately 50–90% of children with OMS-NB have persistent neurological problems, such as late cognitive and neuropsychological sequelae, even after immunological and oncological treatment (12,13). Research documenting these deficits is limited, however. And these problems are the main factors influencing the quality of life of these children.

Here we aimed to review the long-term neurological sequelae of children with OMS-NB, and analyze the risk factors for neurological sequelae. We present the following article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-21-519/rc).

Methods

Study participants

We undertook a retrospective review of children with OMS-NB in Peking University First Hospital from May 2011 to November 2019. The medical records of the children were reviewed. All children were tested by Gesell Developmental Schedules (GDS) within half to one year after first on-site oncology treatment period.

All participants included in this study were diagnosed with OMS-NB by neurologists and hematologists, and were given multidisciplinary treatment in our hospital. Participants were excluded if they refused treatment or follow-up after they were diagnosed with OMS-NB.

Data was collected by trained researchers from the medical records regarding age at onset, gender, oncological status (tumor primary site, tumor histopathology, tumor stage), treatments, neurological symptoms (opsoclonus, myoclonus and ataxia) and neurological sequelae (behavioral changes, language impairment, motor retardation and cognitive disorder).

OMS-NB diagnostic criteria

The diagnostic criteria of OMS-NB were the presence of at least two of the following three features with imaging-proven NB as a requirement: (I) opsoclonus; (II) myoclonus or ataxia; and (III) a behavioral change or sleep disturbance. NB was ultimately diagnosed by tumor histopathological analysis.

Multidisciplinary treatment

Once OMS-NB were diagnosed, the multidisciplinary treatments were applied, including chemotherapy (preoperative and postoperative), surgery, radiotherapy (postoperative) and rehabilitation treatment. The chemotherapy regimens applied at our hospital are Study Group of Japan for Advanced Neuroblastoma (JANB91) protocol (14).

Neurological sequelae

Neurological sequelae in this study were consisted of behavioral changes, cognitive disorder, language impairment and motor retardation. Neurological sequelae were assessed using the GDS within half to one year after first on-site oncology treatment period. Neurological outcomes were classified into 2 groups according to the developmental quotient (DQ) scores of each field: delay, if DQ <85 and normal, if DQ ≥85.

Statistical analysis

Data was expressed as number, proportion; median and range when the distribution was non-normal. For comparisons of categorical variables, the likelihood-ratio test was used. For comparisons of continuous or rank variables, the *t*-test was used. The level of significance for all statistical tests was $P<0.05$. Statistical analyses were conducted using SPSS (IBM SPSS Statistics 20, Chicago, IL, USA).

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Medical Ethics Committee of Peking University First Hospital (No. 2019144). The patients' family members were aware of and agreed to this study, and signed the relevant informed consent.

Table 1 Clinical features of OMS-NB children

Clinical features of OMS-NB	Value
Total number of children	14
Gender (male/female) (n)	9:5
Months of age at OMS onset (median; range)	20; 13–54
Months of age at OMS-NB diagnosis (median; range)	29; 15–65
Motor impairment at OMS onset (n)	
Mild	3/14
Moderate	4/14
Severe	7/14
Duration of OMS symptoms (median; range)	15; 5–48
Location of primary tumor (n)	
Thoracic	1/14
Abdominal	13/14
Adrenal	7/13
Extra-adrenal	6/13
INRG staging at NB detected (n)	
L1	7/14
L2	7/14
Pathology of NB (n)	
Ganglioneuroblastoma	10/14
Ganglioneuroma	3/14
neuroblastoma	1/14

OMS, opsoclonus myoclonus syndrome; NB, neuroblastoma; INRG, International Neuroblastoma Risk Group.

Results

Patients

We identified 14 children with OMS-NB, as shown in *Tables 1*,*2*. The male/female ratio was 9:5, median age at the onset of disease was 20 months (range, 13–54 months). All children developed normally before the onset of OMS, and median age of OMS-NB diagnosis was 29 months (range,15–65 months).

Neurological symptoms

At the onset of OMS, myoclonus and ataxia were seen in all 14 children, opsoclonus were observed in 10/14 children. Eleven/14 children had irritability and sleep disturbance. Five/12 children exhibited language impairment (excluding two children who were unable to speak fluently at the onset of OMS). During the whole disease course, ataxia, opsoclonus, myoclonus, sleep disturbances and irritation were observed in all 14 children, while language impairment were detected in 9/14 children.

At the onset of OMS, 7/14 children with severe motor impairment were unable to sit, 4/14 children with moderate motor impairment were unable to stand but could sit without support. Only 3/14 children with mild motor impairment were able to stand with slightly wide-base. Excluding 1/14 child (patient 11) with tumor recurrence, the median durations of OMS symptoms were 15 months (range, 5–48 months) (*Table 1*).

Oncological state

All 14 children underwent chest and abdomen computed tomography (CT) for NB detection. Thoracic NB was detected in 1/14 child and abdominal NB was detected in 13/14 children. Among the 13 children with abdominal NB, the adrenal gland NB was detected in 7/13, while the extra-adrenal gland NB was detected in the other 6/13. Assessed by International Neuroblastoma Risk Group (INRG) of the first CT results 7/14 had stage L1 NB, and the other 7/14 had stage L2 NB. One/14 child (patient 11), who had L2 NB at first, suffered tumor relapse manifesting as lymph node, bone, bone marrow and pancreas metastases. According to the pathology results of the tumor of the 14 children, 10/14 were diagnosed as ganglioneuroblastoma, 3/14 as ganglioneuroma and 1/14 as NB (*Table 1*). Seven cases were tested for *MYCN* amplification, only one was positive. Five/14 children were tested for 1pLOH (loss of heterozygosity) and 11p23, none was positive.

Treatments

Before NB detection, 10/14 children received immunotherapy. Methylprednisolone (4/10), prednisone (6/10), adrenocorticotropic hormone (1/10), intravenous immunoglobulin (8/10) and rituximab (1/10) were applied. OMS symptoms in these 10 children all improved, but relapses occurred at the weaning off immunotherapy. After NB detection, 7/14 children received preoperative chemotherapy. All 14 children underwent surgery, and 2/14 of these children had microscopic residual disease (MRD). Eleven/14 children received postoperative chemotherapy. Only patient 11 received secondary surgery and 21 rounds

Table 2 Treatment of children with OMS-NB (N=14)

Patient No.	Gender	Age at OMS onset (months)	Stage (INRG)	Immune therapy	Tumor resection	Course of chemotherapy	
						Pre-operative	Post-operative[a]
1	Male	20	L1	I, M	CR	0	3
2	Male	27	L1	M, P	CR	0	0
3	Female	16	L1	I, A, M, R	CR	0	4
4	Male	54	L2	P	CR	0	10
5	Female	13	L2	–	CR	1	6
6	Female	24	L1	–	MRD	0	0
7	Male	19	L2	–	CR	0	6
8	Male	16	L2	I	CR	4	6
9	Male	21	L1	I, P	CR	0	6
10	Female	24	L1	I, M, P	CR	2	0
11	Male	39	L2	–	CR	4	8
12	Male	14	L2	I	CR	2	4
13	Female	18	L2	I, P	MRD	2	3
14	Male	22	L1	I, P	CR	1	2

[a], the courses of post-operative chemotherapy were counted before relapse if the patient suffered relapse. OMS, opsoclonus myoclonus syndrome; NB, neuroblastoma; INRG, International Neuroblastoma Risk Group; CR, complete resection; MRD, microscopic residual disease; M, methylprednisolone; I, intravenous immunoglobulin; P, prednisone; A, adrenocorticotropic hormone; R, rituximab.

of chemotherapy because of the recurrence of NB (as shown in *Table 2*).

Neurological sequelae

All children were tested by GDS within half to one year after first on-site oncological treatment period. Thirteen children had behavioral changes (13/14, 93%), 11 children had language impairment (11/14, 79%), four children had motor retardation (4/14, 29%) and only two children (2/14, 14%) had cognitive disorder. The risk factors for neurological sequelae are listed in *Table 3*. According to single factor analysis, females (P<0.001) and children with residual tumors (P<0.05) tended to reveal motor retardation. Children with non-adrenal-gland-located NB (P<0.05) tend to reveal language impairment. There were no obvious factors that had a statistical relationship with cognitive disorder or behavioral changes.

Up to the last follow-up, GDS were not applicable for most children because of their age. Therefore, the neurological sequelae were assessed through academic performance from their parents. The median interval between the onset of OMS and last follow-up was 62 months (range, 12–102 months). Except for one child with tumor and OMS recurrence (patient 11), all 13 children could study in ordinary schools, 2/13 children had poor academic performance and 11/13 children had good academic performance. Patient 11 died due to NB relapse.

Discussion

According to previous studies, the male-to-female ratio for OMS is around 1:2 or lower, showing OMS with a female predominance (13,15). However, in our study, OMS-NB tended to occur in males. Their median age at onset was 20 months (range, 13–54 months), similar to the onset age in other reports, ranging from 6 months to 4 years (16,17). On comparing the primary location of tumor in our cohort, a 13:1 ratio of abdominal: thoracic tumors were observed showing OMS-NB with an abdominal predominance. A similar predilection is expressed by Pranzatelli *et al.* in their study (17). Histopathologic characteristics of the tumors associated with OMS reveal features of low-risk group. Majority of them are ganglioneuroblastoma. Our series has

Table 3 Risk factors of neurologic sequelae

Feature	Cognitive disorder (N/Y), n1/n2 (n1%/n2%)	Motor retardation (N/Y), n1/n2 (n1%/n2%)	Language impairment (N/Y), n1/n2 (n1%/n2%)	Behavioral changes (N/Y), n1/n2 (n1%/n2%)
Age				
≤18 months	4/1 (80.0/20.0)	2/3 (40.0/60.0)	1/4 (20.0/80.0)	0/5 (0/100.0)
>18 months	8/1 (88.9/11.1)	8/1 (88.9/11.1)	2/7 (22.2/77.8)	1/8 (11.1/88.9)
Gender				
Male	8/1 (88.9/11.1)	9/0 (100.0/0)	3/6 (33.3/66.7)	1/8 (11.1/88.9)
Female	4/1 (80.0/20.0)	1/4 (20.0/80.0)**	0/5 (0/100.0)	0/5 (0/100.0)
The interval between OMS onset and NB detection				
≤6 months	8/0 (100.0/0)	6/2 (75.0/25.0)	2/6 (25.0/75.0)	0/8 (0/100.0)
>6 months	4/2 (66.7/33.3)	4/2 (66.7/33.3)	1/5 (16.7/83.3)	1/5 (16.7/83.3)
Stage				
L1	6/1 (85.7/14.3)	4/3 (57.1/42.9)	2/5 (28.6/71.4)	1/6 (85.7/14.3)
L2	6/1 (85.0/14.3)	6/1 (85.7/14.3)	1/6 (85.7/14.3)	0/7 (0/100.0)
Residual tumor				
Y	1/1 (50.0/50.0)	0/2 (0/100.0)	0/2 (0/100.0)	0/2 (0/100.0)
N	11/1 (91.7/8.3)	10/2 (83.3/16.7)*	3/9 (25.0/75.0)	1/11 (8.3/91.7)
Site				
AD	6/1 (85.7/14.3)	6/1 (85.7/14.3)	3/4 (42.9/57.1)	1/6 (14.3/85.7)
NAD	6/1 (85.7/14.3)	4/3 (57.1/42.9)	0/7 (0/100.0)*	0/7 (0/100.0)
Histopathology	10/2 (83.3/16.7)	8/4 (66.7/33.3)	3/9 (25.0/75.0)	1/11 (8.3/91.7)
NNB	2/0 (100.0/0)	2/0 (100.0/0)	0/2 (0/100.0)	0/2 (0/100.0)
NB				
Treatment				
CT	10/2 (83.3/16.7)	11/1 (91.7/8.3)	1/11 (8.3/91.7)	1/11 (8.3/91.7)
NCT	2/0 (100.0/0)	1/1(50.0/50.0)	0/2 (0/100.0)	0/2 (1/100.0)
Duration of OMS symptom				
≤15 months	6/2 (75.0/25.0)	6/2 (75.0/25.0)	0/8 (0/100.0)	0/8 (1/100.0)
>15 months	0/6 (0/100.0)	4/2 (66.7/33.3)	3/3 (50.0/50.0)	1/5 (16.7/83.3)

*, P<0.05; **, P<0.001. Y, yes; N, no; OMS, opsoclonus myoclonus syndrome; NB, neuroblastoma; AD, adrenal gland; NAD, non-adrenal gland; NNB, non-NB; CT, chemotherapy; NCT, nonchemotherapy.

similar results, with 10 of the 14 cases showing features of ganglioneuroblastoma and 3 cases showing ganglioneuroma. Further, NB was identified only in 1/14 children. Only 1/14 children had a positive *MYCN* amplification.

OMS-NB was a rare disease and not be well-known by doctors who were not neurologist. Some children were misdiagnosed by their primary care doctors as acute cerebellar ataxia before admission to our hospital. Opsoclonus is a vital symptom to distinguish OMS from acute ataxia. Opsoclonus was not observed in some patients of our study, this might be neglected by their parents or primary care doctors who were not neurologist. In Mitchell *et al.*, the interval between OMS onset and diagnosis ranged from 2 days to 14 months (18). In our study, the

median age at the onset of disease was 20 months (range, 13–54 months), and median age of OMS-NB diagnosis was 29 months (range, 15–65 months). However, few previous studies reported the recovery rate of neurological symptoms. Based on our observations, the median durations of OMS symptoms were 15 months (range, 5–48 months).

Unlike neurological symptoms, the outcomes of neurological sequelae were relatively unfavorable. In previous studies, the majority of children experienced resolution of opsoclonus, myoclonus and ataxia, but 60–70% had significant, long-term neurological sequelae (11,18). In our study, approximately 93% children leave some neurological sequelae.

Rudnick *et al.* suggest that age, chemotherapy treatment may not change the risk for developing late sequelae (11), which is consistent with our results. In Takama *et al.*, early detection and treatment of NB in OMS might provide favorable neurological outcomes (15), but other reports have not found this relationship (10,19). De Grandis *et al.* found a borderline negative effect (P=0.075) of a longer interval to OMS-NB diagnosis on cognitive sequelae (13). In our study, the interval between OMS onset and OMS-NB diagnosis was also longer in the cognitive disorder group, although no significant association was found. Krug *et al.* reported that tumor resection showed no relevance to the neurological symptoms or sequelae (12). However, we found that if the tumor was resected completely, motor retardation was less likely to occur. Therefore, if the tumor is found to be difficult to completely remove, we suggest reducing the tumor size before surgery by means of preoperative chemotherapy. More studies of more cases at a longer time-scale will be conducted. In addition, we found that females tended to reveal motor retardation, which indicates that we should pay more attention to the motor problems of females with OMS-NB and suggest female patients receive motor rehabilitation as early as possible. In our research, non-adrenal-gland-located tumor were the main risk factor for language impairment, so we suggest patients with non-adrenal-gland-located tumor concentrate on the language ability.

In conclusion, this report shows that children with OMS-NB have favorable outcomes in terms of neurological symptoms. During the acute stage, myoclonus and ataxia are more easily observed than opsoclonus in OMS-NB children. In this study, the median durations of OMS symptoms were 15 months (range, 5–48 months). Approximately 93% children had some neurological sequelae. Children with features like female sex, residual tumor and non-adrenal-gland-located tumor tend to have neurological sequelae more frequently. There were no obvious factors that had a statistical relationship with cognitive disorder or behavioral changes. Limitations of this study include the small sample size and the retrospective nature of the study. Therefore, prospective studies are urgently needed.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-21-519/rc

Data Sharing Statement: https://tp.amegroups.com/article/view/10.21037/tp-21-519/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-21-519/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by medical ethics committee of Peking University First Hospital (No. 2019144). The patients' family members were aware of and agreed to this study, and signed the relevant informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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