Original Article

Comparison of mediastinal and non-mediastinal neuroblastoma and ganglioneuroblastoma associated with opsoclonus-myoclonus syndrome: a systematic review and meta-analysis

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Background: Neuroblastoma is the most common malignancy in children younger than seven years of age and is the most frequent extracranial solid tumor that occurs in childhood. While opsoclonus–myoclonus syndrome (OMS), a paraneoplastic neurologic syndrome, affects 2–3% of children with neuroblastoma, and the percentage of mediastinal localization of the tumor is 49%. The objective of this study was to identify and characterize features of the OMS syndrome and treatments of mediastinal and non-mediastinal neuroblastoma associated with OMS.

Methods: A systematic review of the literature was performed using PubMed, Medline, Web of Science, Embase and Cochrane. The search has no limit on date with the last search done on Dec 31, 2020. There is no publication restrictions or study design filters applied in the search.

Results: Fifty-five out of 242 papers were identified and met our study eligibility. There were 77 cases found (28 cases had Mediastinal neuroblastoma, and 49 cases had non-mediastinal neuroblastoma). Data from trials showed that cases with mediastinal neuroblastoma who seemed to have undergone less treatment for OMS [rate ratio (RR) 0.41 (95% CI: 0.22–0.76)] had resulted in decreasing persistent neurologic symptoms [RR 0.31 (95% CI: 0.10–0.96)].

Conclusions: Children who have OMS and mediastinal neuroblastoma may be associated with more favorable clinical and biological characteristics and better outcomes than children who have OMS and non-mediastinal neuroblastoma, and they are more likely to present with a single neurological symptom at first. The OMS in mediastinal neuroblastoma might also be treated effectively through resection of the tumor followed by appropriate radiotherapy and chemotherapy, and no long-term treatments of OMS is indicated.

Keywords: Thorax/mediastinal neuroblastoma; non-mediastinal neuroblastoma; opsoclonus-myoclonus syndrome (OMS); pediatric surgery; treatments

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Introduction

Neuroblastoma is the most common extracranial solid tumors occurring in children. The median age at diagnosis is 16 months, and 95% of cases are diagnosed before 7 years of age (1). The neoplasm grows from progenitor cells of the sympathetic nervous system and can be detected anywhere along the sympathetic neurological circuit: retroperitoneally (65%), in the adrenal glands (40%), mediastinally (15%), cervically (11%), and pelvically (3%) (2). Children with opsoclonus-myoclonus syndrome (OMS) are typically presented with acute or subacute ataxia between 6 and 36 months of age and they are unable to walk and/or sit (3). This is accompanied by severe irritability and opsoclonus which appears at variable times from the initial onset to as late as a few weeks after the onset of the motor symptoms (4). In 1968, Dyken and Kolar described the association of OMS with occult neuroblastoma (5). An association between solid neuroblastoma and OMS was actually first described in a paper by Cushing *et al.* on the spontaneous transformation of neuroblastoma to ganglioneuroma in 1927—a fact that is only appreciated recently (6). OMS occurs in 2–3% of patients with neuroblastoma (7), but neuroblastoma is found in as many as 50% of children who are diagnosed with OMS (8). The percentage of mediastinal localization of the tumor (49%) is much higher compared with neuroblastomas without OMS (9). This review compared the different localization of the tumor in order to identify and characterize features of the OMS syndrome and treatments between mediastinal and non-mediastinal neuroblastoma associated with OMS. We present the following article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1120/rc) (10).

Methods

Standard systematic review methodology was employed. A systematic review of case reports and case series published in PubMed, Medline, Web of Science, Embase and Cochrane. The search has no limit on date with the last search done on Dec 31, 2020. There is no publication restrictions or study design filters applied in the search. The search strategy for those databases was as follows: (neuroblastoma [all fields]) AND (opsoclonus-myoclonus syndrome [all fields]). A hand search was performed in all five databases.

Inclusion criteria included well-described OMS with exact tumor location, treatments and outcome. As OMS with neuroblastoma is rare, all the cases are included in case reports.

The results for each group are presented as the mean ± standard deviation ($\overline{x} \pm s$). The log-rank was observed minus expected (o–e) statistics, one from each trial, and their variances (v), were summed to produce, respectively, a grand total was observed minus expected (G) and its variance (V). The one-step estimate of the log of the event rate ratio is G/V. The χ^2 test statistic (χ^2n–1) for heterogeneity between n trials is S–(G^2/V), where S is the sum over all the trials of $(o-e)^2/v$. Heterogeneity of rate ratios among multiple subgroups was defined by baseline characteristics and was investigated by a global heterogeneity test, which helped to avoid misinterpreting false positive results arising from multiple comparisons.

Statistical analysis

Statistical analysis was conducted by STATA version 12.0. Relative risk (RR) was applied for dichotomous variables. The I^2 statistic was used to test the degrees of heterogeneity, the P value of I^2<0.05 was used to indicate high heterogeneity. The random-effects model was applied to pool the high heterogeneity results and a fixed-effects model was used for low heterogeneity (P value of I^2 >0.05). P values <0.05 were considered to be statistically significant.

Results

Two hundred and forty-two papers were identified including the hand search yielding 30 papers. Fifty-nine papers were duplicate papers from different search engines, 70 papers were excluded after title and abstract evaluation, and 58 papers were excluded after full-text review because they did not meet the inclusion criteria (*Figure 1*). Among the 55 papers included, some were case series with multiple cases, and the total number of cases analyzed was 77.

Children with OMS and neuroblastoma

We focused on gender, age of onset, tumor location, pathology, neurological symptoms, treatments and prognosis in the 77 children identified through our search, these clinical and biological characteristics were listed in chronological order and was displayed in *Table 1*. The tumor location included mainly the abdomen and the mediastinum. Tumors on the neck and the pelvic area were rare. Neurological symptoms identified from the 77 cases

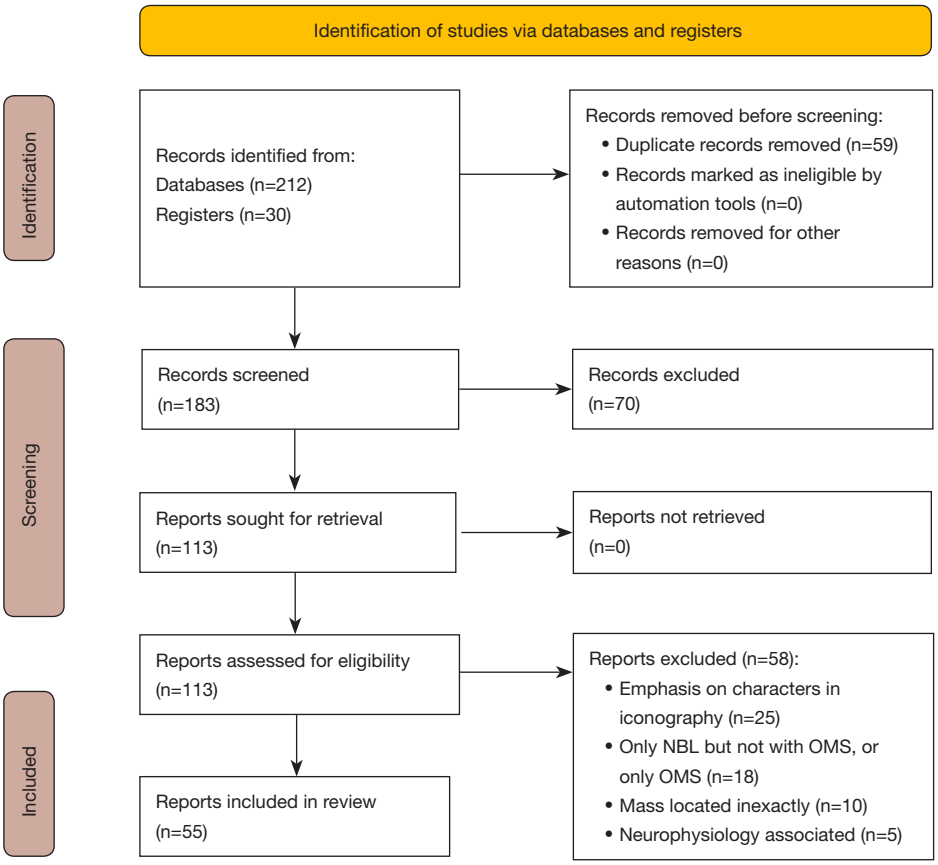

Figure 1 Adapted PRISMA flow diagram, showing the number of papers identified in the initial search, numbers excluded for various reasons and the final number of papers which are the basis of the data presented.

were mainly from these four aspects: ataxia, opsoclonus, myoclonus, and irritability. The other clinical symptoms included neonatal lupus, type 1 diabetes mellitus (T1DM), constipation and etcetera. Biopsy or resection, radiotherapy, chemotherapy and treatments of OMS were also included in the treatments. Tumor prognosis was reported as recurrence and non-recurrence, and the prognosis of neurological symptoms was mainly divided into three categories: no symptom, improved symptom, and persistent symptom. No symptom is defined as positive response to treatments of OMS; improved symptom is defined as patients showed benefits from the treatment but OMS is not in complete remission; persist symptom is identified as no response to treatment. The average age at diagnosis for the 77 cases with known age was 21.3±11.8 months; they consisted of thirty-two males and forty-five females. The tumors were located in the mediastinum, retroperitoneum, neck, and pelvic, it accounted for 36% (n=28), 55% (n=42), 4% (n=3) and 5% (n=4) of all the cases, respectively. See *Table 1* for the detailed information with all reported cases (n=77) that met the inclusion criteria.

Comparisons of children with OMS and neuroblastoma in different locations

Table 2 summarizes the syndromes with all the reported cases (n=77) that met the inclusion criteria: mediastinal neuroblastoma (n=28), non-mediastinal neuroblastoma (n=49).

Characters in mediastinal and non-mediastinal neuroblastoma—subgroup analyses

There were no significant differences in overall characters in mediastinal neuroblastoma and non-mediastinal neuroblastoma trials [rate ratio (RR) 1.07 (95% CI: 0.85–

Table 1 References in the literature to children with OMS and neuroblastoma

Author	Sex	Age of onset	Location of tumor	Pathology	Neurologic symptom	Treatments	Outcome (symptom & tumor)
Shtarbanov *et al.*, 2020 (11)	F	21m	T1-3, posterior mediastinum	Neuroblastoma	Ataxia; opsoclonus; myoclonus[a]	Surgery; chemotherapy	Symptom improved & no evidence of tumor recurrence
	F	21m	The left carotid space	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; chemotherapy	No symptom remission & no evidence of tumor recurrence
	F	18m	Retroperitoneum	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery	Symptom improved & no evidence of tumor recurrence
Kaur *et al.*, 2019 (12)	M	24m	Left posterior mediastinum	Not reported[b]	Ataxia; opsoclonus; myoclonus; irritability	Without surgery	Not reported
Storz *et al.*, 2019 (13)	F	7m	Left posterior mediastinum	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; T.O[a]	Symptom improved & no evidence of tumor recurrence
	M	13m	The left adrenal gland	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; T.O	Persistent symptom & no evidence of tumor recurrence
	M	13yr11m	T11-L1, the right paravertebral	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; T.O	No symptom & no evidence of tumor recurrence
Greensher *et al.*, 2018 (14)	M	14m	Abdomen	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Biopsy; chemotherapy; T.O	Symptom improved & no evidence of tumor recurrence
Sharawat *et al.*, 2018 (15)	M	15m	T10-L2, vertebrae	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability (neonatal lupus)	Surgery; T.O	Symptom improved & no evidence of tumor recurrence
Johnston *et al.*, 2018 (16)	M	10m	(INSS IVs) the neck	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; T.O	Symptom improved & no evidence of tumor recurrence
	F	21m	(INSS I) the left suprarenal gland	Neuroblastoma	Ataxia[a]; opsoclonus; myoclonus	Surgery; chemotherapy; T.O	Persistent symptom & no evidence of tumor recurrence
Mizuno *et al.*, 2017 (17)	F	14m	The right adrenal gland	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus; (laryngeal stridor)	Biopsy; chemotherapy	Symptom improved & tumor remain
Wu *et al.*, 2017 (18)	F	16m	The retroperitoneal area	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; T.O	Symptom improved & no evidence of tumor recurrence
Meena *et al.*, 2016 (19)	M	26m	T6-8 right posterior mediastinum	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; chemotherapy; T.O	Symptom improved & no evidence of tumor recurrence
	F	34m	T6-8, left posterior mediastinum	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Without surgery	No symptom & no evidence of tumor recurrence
	M	22m	Abdomen	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; chemotherapy; T.O	Symptom improved & no evidence of tumor recurrence
	F	34m	L2-3, left upper psoas muscle extending into left neural foramen	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; chemotherapy; T.O	Symptom improved & no evidence of tumor recurrence
	M	36m	Abdomen	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; chemotherapy; T.O	Persistent symptom & died of febrile encephalopathy (not related to disease)
	F	34m	Abdomen	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	T.O	No symptom & tumor recurrence 2 years later
Ghia *et al.*, 2016 (20)	F	17m	T3-8, right posterior mediastinum	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability; (T1DM)	Surgery; T.O	Symptom improved & no evidence of tumor recurrence
Sweeney *et al.*, 2016 (21)	F	11yr	L2-4, vertebral levels	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus[a]	Biopsy; chemotherapy; T.O	Persistent symptom & tumor remain
Toyoshima *et al.*, 2016 (22)	M	2yr	The left adrenal gland	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; T.O	No symptom & no evidence of tumor recurrence
Amini *et al.*, 2016 (23)	F	6yr	(INSS IV) para-aortic, abdomen	Neuroblastoma	Ataxia; Opsoclonus; myoclonus; (constipation)	Surgery; radiotherapy; T.O	Persistent symptom & tumor recurrence
Galgano *et al.*, 2015 (24)	F	21m	The pancreatic body	Neuroblastoma	Ataxia; opsoclonus[a]; myoclonus	Biopsy; chemotherapy	No symptom & no evidence of tumor recurrence
Hu *et al.*, 2015 (25)	M	5m	The left adrenal gland	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; chemotherapy	No symptom & no evidence of tumor recurrence
Sinha *et al.*, 2014 (26)	F	1yr6m	(INSS IIa) T10-L1, the right para-spinal	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; T.O	No symptom & no evidence of tumor recurrence
Krivochenitser *et al.*, 2014 (27)	F	2yr	The right suprarenal gland	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; T.O	No symptom & no evidence of tumor recurrence
Maranhão *et al.*, 2013 (28)	F	17m	T3-6, right posterior mediastinum	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery	Symptom improved & no evidence of tumor recurrence
Joshi *et al.*, 2013 (29)	M	0.5m	T3-5, posterior mediastinum	Neuroblastoma	Ataxia; opsoclonus[a]; myoclonus	Surgery; T.O	No symptom & no evidence of tumor recurrence
	M	26m	(INSS IV) T1-4, posterior mediastinum	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Biopsy; chemotherapy	Symptom improved & tumor remain
Morales La Madrid *et al.*, 2012 (30)	F	14m	(INSS I) pelvic	Neuroblastoma	Ataxia; opsoclonus; myoclonus; (constipation)	Surgery; T.O	Persistent symptom & no evidence of tumor recurrence
Oguma *et al.*, 2012 (31)	M	11m	(INSS I) retroperitoneal	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; T.O	Symptom improved & no evidence of tumor recurrence
Kuyama *et al.*, 2012 (32)	F	4y4m	The right adrenal gland	Ganglioneuroblastoma	Ataxia[a]; opsoclonus; myoclonus	Surgery	Symptom improved & no evidence of tumor recurrence
Pranzatelli *et al.*, 2012 (33)	M	22m	The hilus of the right kidney	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; T.O	Persistent symptom & no evidence of tumor recurrence
Paliwal *et al.*, 2010 (34)	M	8m	(INSS IIa) retroperitoneal pelvic	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; T.O	Symptom improved & tumor recurrence
Corapcioglu *et al.*, 2008 (35)	M	48m	right posterior mediastinum	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; T.O	No symptom & no evidence of tumor recurrence
Stefanowicz *et al.*, 2008 (36)	F	15m	The right suprarenal gland	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery	Persistent symptom & no evidence of tumor recurrence
	F	16m	The retroperitoneal area	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; chemotherapy	No symptom & no evidence of tumor recurrence
	M	4yr	The right suprarenal gland	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; chemotherapy; T.O	Symptom improved & no evidence of tumor recurrence

Table 1 (*continued*)

Table 1 (*continued*)

Author	Sex	Age of onset	Location of tumor	Pathology	Neurologic symptom	Treatments	Outcome (symptom & tumor)
	F	3.5yr	The right suprarenal gland	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; chemotherapy	Symptom improved & no evidence of tumor recurrence
Burke *et al.*, 2008 (37)	M	3yr6m	Above the right kidney	Ganglioneuroblastoma	Ataxia[a]; opsoclonus; myoclonus	Surgery; T.O	Symptom improved & no evidence of tumor recurrence
Bell *et al.*, 2008 (38)	F	19m	The right renal hilum	Ganglioneuroblastoma	Ataxia[a]; opsoclonus; myoclonus	Surgery; T.O	Symptom improved & no evidence of tumor recurrence
Ertle *et al.*, 2008 (39)	M	33m	(INSS III) T10-L1, the right para-spinal	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; chemotherapy; T.O	No symptom & no evidence of tumor recurrence
Badaki *et al.*, 2007 (40)	F	15m	The right presacral	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery	Loss of follow-up
Cardesa-Salzmann *et al.*, 2006 (41)	F	20m	(INSS I) right posterior mediastinum	Ganglioneuroblastoma	Ataxia[a]; opsoclonus; myoclonus (EBV+)	Surgery	No symptom & no evidence of tumor recurrence
Chang *et al.*, 2006 (42)	M	4yr	The left adrenal gland	Neuroblastoma	Ataxia[a]; opsoclonus; myoclonus; irritability	Surgery; T.O	No symptom & no evidence of tumor recurrence
Armstrong *et al.*, 2005 (43)	M	14m	(INSS II) posterior mediastinum	Ganglioneuroblastoma	Ataxia[a]; Opsoclonus; Myoclonus	Surgery; T.O	No symptom & no evidence of tumor recurrence
Gesundheit *et al.*, 2004 (44)	F	19m	The right adrenal gland	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus; irritability; (VIP associated diarrhea)	Surgery	Persistent symptom & no evidence of tumor recurrence
Emir *et al.*, 2003 (45)	M	12m	(INSS IIb) the left suprarenal gland	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; T.O	No symptom & no evidence of tumor recurrence
Swart *et al.*, 2002 (46)	F	13m	Supraphrenic lesion	Not reported[b]	Ataxia[a]; opsoclonus; myoclonus	Without surgery; radiotherapy; T.O	No symptom & no evidence of tumor recurrence
Maeoka *et al.*, 1998 (47)	F	13m	Posterior mediastinum	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability[a]	Surgery	No symptom & no evidence of tumor recurrence
Veneselli *et al.*, 1998 (48)	M	8m	(INSS III) retroperitoneal	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; chemotherapy	Persistent symptom & no evidence of tumor recurrence
Posada *et al.*, 1998 (49)	F	12m	The level of C7	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; chemotherapy; T.O	Symptom improved & no evidence of tumor recurrence
Janss *et al.*, 1996 (50)	M	29m	The left suprarenal gland	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; T.O	Persistent symptom & no evidence of tumor recurrence
	F	21m	The celiac axis	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; T.O	Persistent symptom & no evidence of tumor recurrence
Fisher *et al.*, 1994 (51)	F	20m	The left adrenal gland	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery	Persistent symptom & no evidence of tumor recurrence
Mitchell *et al.*, 1990 (52)	M	14m	Left posterior mediastinum	Ganglioneuroblastoma	Ataxia[a]; opsoclonus; myoclonus	Surgery; T.O	Symptom improved & no evidence of tumor recurrence
	F	3yr	The left suprarenal gland	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; T.O	Symptom improved & no evidence of tumor recurrence
	F	13m	The vena cava into the right pelvis	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; chemotherapy	No symptom & no evidence of tumor recurrence
	F	15m	The hilus of the left kidney	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus[a]	Surgery; T.O	Symptom improved & no evidence of tumor recurrence
	F	15m	The left periaortic	Ganglioneuroblastoma	Ataxia[a]; opsoclonus; myoclonus	Surgery; T.O	Persistent symptom & no evidence of tumor recurrence
Harel *et al.*, 1987 (53)	F	1yr	L2-3, palpable left to the midline	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus (hypertension)	Surgery; chemotherapy; T.O	Symptom improved & no evidence of tumor recurrence
Kinast *et al.*, 1980 (54)	F	9m	Retroperitoneal	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; T.O	Symptom improved & no evidence of tumor recurrence
Malmström Groth *et al.*, 1972 (55)	F	20m	(INSS I) right posterior mediastinum	Neuroblastoma	Ataxia[a]; opsoclonus; myoclonus; irritability	Surgery; chemotherapy; radiotherapy	Symptom improved & no evidence of tumor recurrence
Leonidas *et al.*, 1972 (56)	F	14m	(INSS II) right posterior mediastinum	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; chemotherapy; radiotherapy	Symptom improved & no evidence of tumor recurrence
Martin *et al.*, 1971 (57)	F	8m	Posterior mediastinum	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Chemotherapy; radiotherapy	No symptom & no evidence of tumor recurrence
Förster *et al.*, 1971 (58)	F	21m	(INSS I) posterior mediastinum	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; chemotherapy; radiotherapy	No symptom & no evidence of tumor recurrence
Moe *et al.*, 1970 (59)	F	13m	(INSS II) right posterior mediastinum	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; chemotherapy; radiotherapy	Symptom improved & no evidence of tumor recurrence
	M	24m	(INSS II) left posterior mediastinum	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; chemotherapy; radiotherapy	Persistent symptom & no evidence of tumor recurrence
Bray *et al.*, 1969 (60)	M	23m	(INSS IV) posterior mediastinum	Ganglioneuroblastoma	Ataxia; opsoclonus; myoclonus[a]; irritability	Biopsy; chemotherapy; radiotherapy	Symptom improved & died of tumor
	M	13m	Left posterior mediastinum	Neuroblastoma	Ataxia; opsoclonus; myoclonus[a]; irritability	Surgery; chemotherapy; radiotherapy	Persistent symptom & no evidence of tumor recurrence
Brissaud *et al.*, 1969 (61)	F	27m	(INSS I) posterior mediastinum	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; chemotherapy; radiotherapy	Symptom improved & no evidence of tumor recurrence
Lemerle *et al.*, 1969 (62)	M	15m	(INSS IV) posterior mediastinum	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; radiotherapy	Symptom improved & tumor recurrence
	F	37m	Posterior mediastinum	Neuroblastoma	Ataxia; opsoclonus; myoclonus	Surgery; chemotherapy	Symptom improved & no evidence of tumor recurrence
Dyken *et al.*, 1968 (5)	F	8m	(INSS II) posterior mediastinum	Neuroblastoma	Ataxia; opsoclonus; myoclonus[a]; irritability	Surgery; radiotherapy	Symptom improved & no evidence of tumor recurrence
Solomon *et al.*, 1968 (63)	M	13m	(INSS II) left posterior mediastinum	Neuroblastoma	Ataxia[a]; opsoclonus; myoclonus[a]; irritability	Surgery; chemotherapy; radiotherapy	Symptom improved & no evidence of tumor recurrence
Davidson *et al.*, 1968 (64)	M	13m	The right lower quadrant of the abdomen	Neuroblastoma	Ataxia; opsoclonus; myoclonus; irritability	Surgery; radiotherapy	Symptom improved & no evidence of tumor recurrence

[a], unitary first symptom of OMS; [b], MRI scan revealed a supraphrenic, paravertebral tumor on the left side most likely resembling a neuroblastoma or ganglioneuroma; [c], treatments of OMS are about ACTH and oral corticosteroids, intravenous immunoglobulin, rituximab, plasmapheresis, et al. OMS, opsoclonus–myoclonus syndrome; ACTH, adrenocorticotropic hormone; M, male; F, female; m, months; yr, years; T.O, treatments of OMS[c]; T1DM, type 1 diabetes mellitus; EBV, epstein-barr virus; VIP, vasoactive intestinal peptide.

Table 2 The comparisons of mediastinal and non-mediastinal neuroblastoma (cases/%)

Characteristics	Mediastinal neuroblastoma (28 cases)	Non-mediastinal neuroblastoma (49 cases)
Sex		
Male	12/42.9	20/40.8
Female	16/57.1	29/59.2
Age at time of neurologic dysfunction (months), mean ± SD	18.4±7.3	23.1±13.4
Unitary first symptom of OMS		
Ataxia	6/21.4	8/16.3
Irritability	1/3.6	0/0
Myoclonus	5/18	2/4.1
Opsoclonus	1/3.6	1/2
None unitary first symptom of OMS	15/53.4	38/77.6
Surgical treatments		
B+C or/and R	2/7.2	5/10.2
S	9/32.1	27/55.1
S+C or/and R	13/46.3	17/34.7
WS	2/7.2	0/0
WS+C or/and R	2/7.2	0/0
Management associated[a]		
Treatments of OMS	8/28.6	34/69.4
None	20/71.4	15/30.6
Neurologic symptoms		
No symptom	9/32.1	13/26.5
Symptom improved	15/53.4	18/36.7
Persistent symptom	3/10.9	17/34.8
Loss of follow-up	1/3.6	1/2
Tumor outcome		
Reoccur or death	3/10.9	4/8.2
Stable disease	24/85.5	44/89.8
Loss of follow-up	1/3.6	1/2
Pathologic examination		
Ganglioneuroblastoma	9/32.1	18/36.7
Neuroblastoma	17/60.7	31/63.3
WS	2/7.2	0/0
Concomitant symptom		
Hypertension	1/3.6	1/2
Constipation	0/0	2/4.1
Laryngeal stridor	1/3.6	1/2
Neonatal lupus	26/92.8	1/2
VIP associated diarrhea		1/2
Not reported		43/87.9

[a], management associated is about treatments of OMS, such as ACTH and oral corticosteroids, intravenous immunoglobulin, rituximab, plasmapheresis, et al. OMS, opsoclonus–myoclonus syndrome; ACTH, adrenocorticotropic hormone; B, biopsy; S, surgery; WS, without surgery; C, chemotherapy; R, radiotherapy; T1DM, type 1 diabetes mellitus; EBV+, Epstein-Barr virus positive; VIP, Vasoactive Intestinal Peptide.

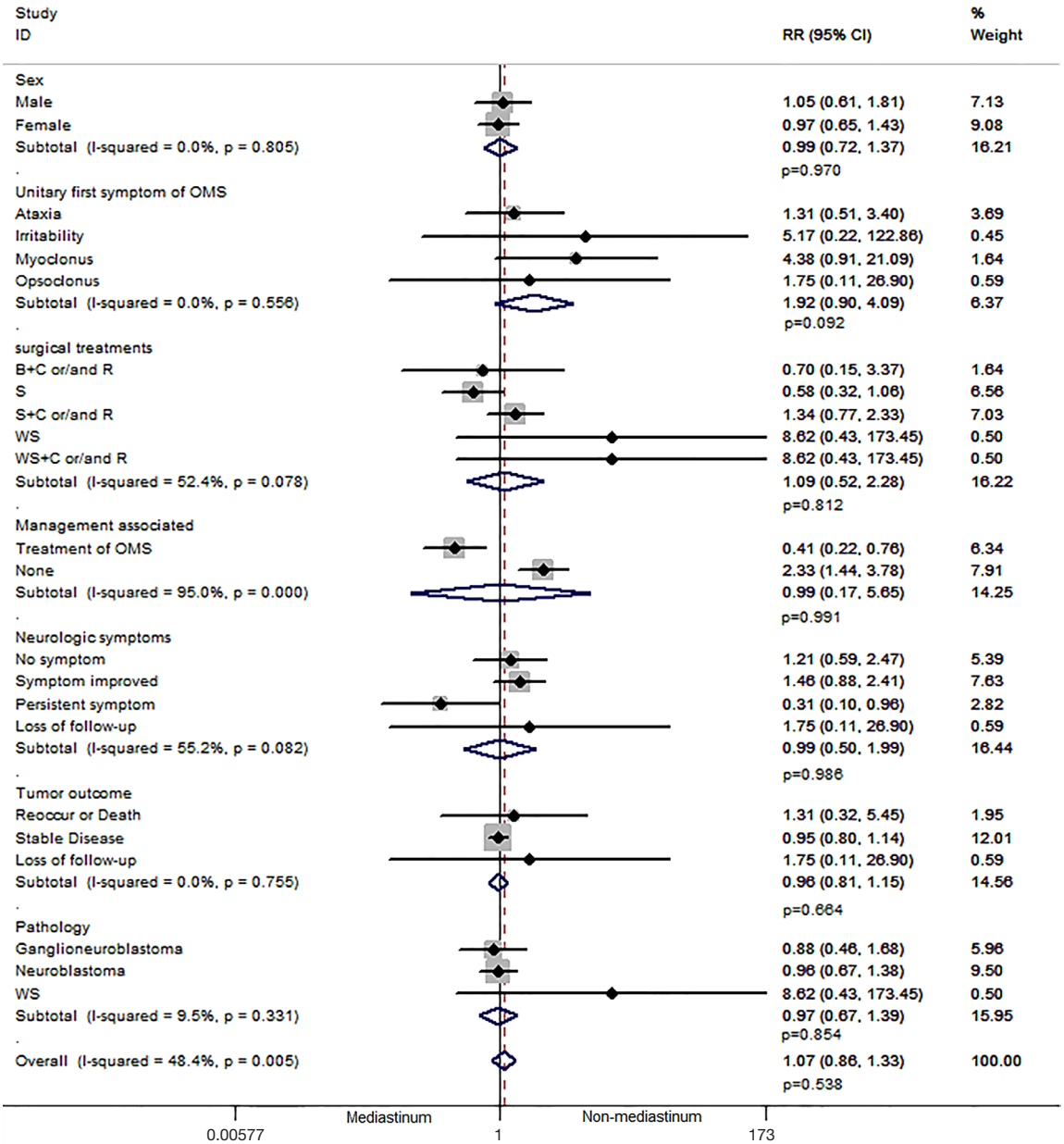

Figure 2 RRs for all trials are indicated by squares and their 95% CIs by horizontal lines. Subtotals and their 95% CIs are represented by diamonds. Squares or diamonds to the left of the solid line indicate mediastinal benefit. RRs, rate ratios; B, biopsy; S, surgery; WS, without surgery; C, chemotherapy; R, radiotherapy.

1.33), P=0.573; *Figure 2*] such as: sex [RR 0.99 (95% CI: 0.72–1.37), P=0.970; *Figure 2*], unitary first symptom of OMS [RR 1.92 (95% CI: 0.90–4.09), P=0.092; *Figure 2*], surgical treatments [RR 1.09 (95% CI: 0.52–2.28), P=0.814; *Figure 2*], treatments of OMS [RR 0.99 (95% CI: 0.77–5.65), P=0.991; *Figure 2*], neurologic symptoms [RR 0.99 (95% CI: 0.50–1.99), P=0.986; *Figure 2*], tumor outcome [RR 0.96 (95% CI: 0.81–1.15), P=0.664; *Figure 2*] and pathology [RR 0.97 (95% CI: 0.67–1.39), P=0.854; *Figure 2*]. However, data from trials showed that cases with mediastinal neuroblastoma seemed to receive less treatments of OMS [RR 0.41 (95% CI: 0.22–0.76); *Figure 2*] and resulted in

decreased persistent neurologic symptoms [RR 0.31 (95% CI: 0.10–0.96); *Figure 2*], which means more cases were in remission.

Discussion

Overall, we found 77 cases of children with neuroblastoma and OMS from literature review. While OMS occurs in 2–3% of patients with neuroblastoma (7), many of these syndromes are rare and most of the cases were case reports. Because the data was obtained through a systematic literature review, the available data in each case report was limited, therefore randomized controlled test was not performed. In Altman and Baehner's study (65), the case reports of 28 neuroblastoma patients who had opso-myoclonus as their presenting feature were reviewed. In comparison to the 30–34% two-year survival rate for the overall population of patients with neuroblastoma, those exhibiting the opso-myoclonus and neuroblastoma combination had a higher tumor-free two-year survival rate of 89.3%. This may be due to the fact that OMS and neuroblastoma were autoimmune in nature which affected the growth and the spread of the tumor.

The average age of those children with OMS in the mediastinal neuroblastoma group and non-mediastinal neuroblastoma group is older than the median age of children with neuroblastoma reported in the literature (1). In our review, most of the cases in the mediastinal neuroblastoma group were reported as stage I-II, while the stages of the tumor in the non-mediastinal group were mostly unknown. The 5-year survival rate of the mediastinal neuroblastoma cases was significantly more favorable than that of the non-mediastinal neuroblastomas. The majority of mediastinal neuroblastoma cases presented at an early stage are associated with favorable prognostic factors (66). We found that the average age between the mediastinal and non-mediastinal neuroblastoma groups had no significant difference (P>0.05). Because of the earlier diagnosis and distinct biological characteristics, a favorable prognosis would suggest less aggressive treatment is needed for these patients (67). The median age and average age of the two groups are both older than one year of age, with only 10 children out of 77 (13%) cases were younger than one year old. Children within one year of age have relatively under-developed autoimmunity, which may be correlated with the lower occurrence of OMS in children of this age (65,68). There are slightly more female children in the mediastinal and non-mediastinal group than males, this is consistent with the reported children who suffer from neuroblastoma but without OMS (66,67,69). Children with OMS are usually presented as a typical OMS, or unitary first symptom such as acute/subacute ataxia (unable to walk and/or sit) (3), this is accounted for 21.4% in the mediastinal group and 16.3% in the non-mediastinal group. Nearly half of the children with mediastinal neuroblastoma and OMS started with a unitary neurological symptom and were then accompanied with severe irritability and opso-myoclonus at later time (46.6%). The guidelines for the treatment of the neuroblastoma do not differ according to the localization of the tumor, from the literature there is no significant difference in the two groups with regards to surgical treatments, radiotherapy and chemotherapy in the literature [RR 1.09 (95% CI: 0.52–2.28), P=0.814; *Figure 2*], and the pathology [RR 0.97 (95% CI: 0.67–1.39), P=0.854; *Figure 2*], and no clear reduction in rates of recurrence (or death) of the tumor [RR 0.96 (95% CI: 0.81–1.15), P=0.664; *Figure 2*]. There is no significant difference in recurrence or death and the survival rate is low. However, the mediastinum group with localized tumor (stage I, II, and III) may be associated with more favorable clinical and biological characteristics and has better outcome (70): the survival rate of the mediastinum group with localized tumor is 100%. The interesting point is, in cases that underwent an incomplete resection of the primary tumors in localized neuroblastoma, the 5-year survival rate of the mediastinal neuroblastoma cases was significantly more favorable than that of the other neuroblastomas (66). Furthermore, we found that only four children in the mediastinal group did not have surgery. Among them, one was lost in follow-up; two of the remaining three cases received only radiotherapy and chemotherapy and the last one did not receive any treatment but was on observation and the tumor and OMS disappeared completely. This is in line with Brodeur GM's theory of "spontaneous regression" by an "anti-tumor immune response". He argued that all children with OMS should have had neuroblastoma, but less than half of the children with OMS were found to have solid tumor due to the spontaneous regression, which was called autoimmunity caused by the existence of the tumor. Brodeur GM reviewed several possible mechanisms of the spontaneous regression of neuroblastoma: (I) neurotrophin deficiency: alterations of TrkA neurotrophin receptor dependence or lack of nerve growth factor (NGF) in the microenvironment; (II) loss of telomerase activity or shortening of telomere; (III) tumor destruction mediated by anti-tumor immune responses in humoral or cellular immunity; (IV) alterations in epigenetic

regulation and other possible mechanisms: Changes in gene methylation or histone modifications (71).

Although treatments of OMS in postoperative cases of the mediastinal group are significantly less than those in the non-mediastinal group [RR 0.41 (95% CI: 0.22–0.76); *Figure 2*], the cases of persistent symptom of OMS in the non-mediastinal group are significantly higher than that in the mediastinal group [RR 0.31 (95% CI: 0.10–0.96); *Figure 2*], which means the number of positive response cases (including complete response and partial response) of neurological symptoms in the mediastinal group is significantly higher than in the non-mediastinal group. Therefore, it may be determined that OMS in mediastinal neuroblastoma is more likely to resolve with the treatment of the primary tumor rather than treating OMS alone.

The pathogenesis of the OMS in neuroblastoma is mainly considered as paraneoplastic syndromes (PNS). It may be due to a paraneoplastic or autoimmune etiology when it is associated with neuroblastoma (72), meaning there may be the presence of an antineuronal antibody cross-reacting with areas of the patient's tumor (51). Various studies have shown that the different antigen-antibody reactions produced by various tumors are closely related to the manifestations of neurological symptoms: Purkinje Cell Antibody (PCA) leads to cerebellar ataxia (73,74), while anti-neuronal nuclear antibody (ANNA) leads to encephalomyelitis and peripheral nervous system disorders (75-80). ANNA-1 and ANNA-2 differ in protein molecular weights (76). ANNA-1 (also known as anti-Hu) is a marker of paraneoplastic autoimmunity associated with small-cell carcinoma (usually of the lung) and peripheral nervous system presentations are most common; ANNA-2 IgG (also known as anti-Ri) is found in patients with small-cell lung carcinoma or breast carcinoma and bind to the central nervous system (76-80). Among all the complications, there were only two cases with constipation in the non-mediastinal neuroblastoma which was associated with the disease itself, and the serum ANNA-1 of the children with constipation was positive (23,30). In some cases, having positive anti-Hu antibody can lead to intestinal dysfunction in children with neuroblastoma, such as constipation, gut dysmotility and even paralytic ileus (23,30,81-83), and is collectively called gastro-intestinal anti-Hu syndrome. It may be because Anti-Hu antibodies has evoked neuronal apoptosis which contributes to the enteric nervous system impairment leading to underlying paraneoplastic gut dysmotility (84), but the incidence rate is only 2 out of 77 cases in our study (2.6%). Despite the fact that anti-Hu antibodies are present in several other presumably paraneoplastic conditions occasionally seen in children with neuroblastoma, no antibody has been identified as etiologic in OMS, even after a great deal of searching by multiple labs.

There are several limitations in this review. Not all case reports were complete with all of the variables of interest: such as the stages of the tumor, MYCN status, tumor location, pathology and survival status. Since cases are rare, we have to include older cases and some cases that were lost in follow-up in the later part of the study period. Due to the various follow-up time, we were unable to produce a survival curve.

In summary, OMS may be possibly associated with the progression of mediastinal and non-mediastinal neuroblastoma (7,71,85-87). We also noted that mediastinal neuroblastoma has a better prognosis than non-mediastinal neuroblastoma in terms of tumor treatments and neurological symptoms.

Conclusions

Mediastinal neuroblastoma with OMS, one of the common types of neurogenic tumors with OMS in children (9), is more likely to present with a single neurological symptom at first, which might be associated with more favorable clinical and biological characteristics and a better outcome than non-mediastinal neuroblastoma. OMS in mediastinal neuroblastoma might also be resolved significantly through resection of the tumor followed by appropriate radiotherapy and chemotherapy, and no long-term treatments of OMS is needed.

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Footnote

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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.

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