UDC 616.27-006.487-053.2+616.831-002

T.I. Stetsenko[1], H.M. Fedushka[2], S.O. Rebenkov[2], T.P. Ivanova[2]

The case of Kinsburn's Encephalopathy in a child with neuroblastoma of posterior mediastinum

[1]Shupyk National Healthcare University of Ukraine, Kyiv
[2]National Children's Specialized Hospital «OKHMATDYT», Kyiv, Ukraine

Modern Pediatrics. Ukraine. (2024). 1(137): 138-142. doi: 10.15574/SP.2024.137.138

For citation: Stetsenko TI, Fedushka HM, Rebenkov SO, Ivanova TP. (2024). The case of Kinsburn's Encephalopathy in a child with neuroblastoma of posterior mediastinum. Modern Pediatrics. Ukraine. 1(137): 138-142. doi: 10.15574/SP.2024.137.138.

Opsoclonus-myoclonus-ataxia syndrome (OMAS) is an autoimmune rare disease of the central nervous system with lesion of the cerebellum and its ligaments.

Purpose — to present a case of the rare Kinsburn's Encephalopathy — OMAS and to attract the attention to its timely diagnosis.

Clinical case. A child at the age of 1 year and 9 months was observed in the neurological department of the National Children's Specialized Hospital «OKHMATDYT». Neurological status: eyes opsoclonus, truncal tremor, ataxia of the cerebellum. There were also changes in behavior and a sleep disorder. She became sick in 1 month after acute respiratory infection. True diagnosis was made: Kinsburn's Encephalopathy — opsoclonus-myoclonus syndrome. A study of the child's immune status was made and, most importantly, computerized tomography (CT) of the whole body. Mediastinal neuroblastoma was diagnosed.

In addition to the diagnosis, the child receive adequate therapy — intravenous immunoglobulin at a dose of 2 g/kg for a 5-day course. On the background of the received therapy, the child was marked with positive dynamics, she began to walk by herself, the atactic syndrome diminished, opsoclonus remained unchanged.

Consequently, the main cause of autoimmune defeat of the nervous system was detected and the child was directed to the further examination and treatment to the Cancer Institute of the National Academy of Medical Science of Ukraine.

Radical removal of the left hemopleura neuroblastoma was made. According to the results of morphological and immunohistochemistry tests, the phenotype obtained in the material of the operation is characteristic of the neuroblastoma (ICD-O code 9500/3), pT1bpN0M0, negative form. In the future, the child continued to receive courses of immunosuppressive therapy.

The research was carried out in accordance with the principles of the Helsinki Declaration. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: neuroblastoma, paraneoplastic syndrome, opsoclonus-myoclonus, Kinsburn's encephalopathy.

Випадок енцефалопатії Кінсбурна в дитини з нейробластомою заднього середостіння

Т.І. Стеценко[1], Г.М. Федушка[2], С.О. Ребенков[2], Т.П. Іванова[2]
[1]Національний університет охорони здоров'я України імені П.Л. Шупика, м. Київ
[2]Національна дитяча спеціалізована лікарня «ОХМАТДИТ», м. Київ, Україна

Опсоклонус-міоклонус-атаксія синдром — автоімунне рідкісне захворювання центральної нервової системи з ураженням мозочка та його зв'язків.

Мета — навести випадок рідкісної енцефалопатії Кінсбурна — опсоклонус-міоклонус-атаксія синдрому; привернути увагу до її вчасної діагностики.

Клінічний випадок. У неврологічному відділенні Національної дитячої спеціалізованої лікарні «ОХМАТДИТ» обстежено дівчинку віком 1 рік 9 міс. У неврологічному статусі виявлено опсоклонус очей, тремор тулуба, атаксію мозочкову. Крім того, відмічено порушення поведінки — вередування, неспокій, агресію щодня, яких раніше не було, а також порушення сну. Дитина захворіла за 1 місяць після гострої респіраторної вірусної інфекції.. Встановлено правильний діагноз «Енцефалопатія Кінсбурна — опсоклонус-міоклонус-атаксія синдром». Проведено імуноцитологічне обстеження. Проведено комп'ютерну томографію органів грудної клітки та живота, виявлено часту причину цієї хвороби — нейробластому.

Після діагностування дитині одразу призначено адекватну терапію — внутрішньовенний імуноглобулін у дозі 2 г/кг (курсом 5 діб). На тлі отримуваної терапії відзначено позитивну динаміку — дитина почала самостійно ходити, зменшився атактичний синдром, однак опсоклонус залишився без змін.

Отже, виявлено основну причину автоімунного ураження нервової системи, дитину направлено на дообстеження та лікування до Інституту раку НАМН України.

Виконано радикальне видалення нейробластоми. За результатами морфологічного та імуногістохімічного досліджень у матеріалі операції отримано фенотип, характерний для нейробластоми (ICD-O code 9500/3), pT1bpN0M0, N-тус негативна форма.

Дослідження виконано відповідно до принципів Гельсінської декларації. На проведення досліджень отримано інформовану згоду батьків дитини.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: нейробластома, паранеопластичний синдром, опсоклонус-міоклонус, енцефалопатія Кінсбурна.

Introduction

Opsoclonus-myoclonus-ataxia syndrome (OMAS) (G 25.3 according to ICD-10) or Kinsburn's Encephalopathy is an autoimmune rare disease of the central nervous system with lesion of the cerebellum and its ligaments. OMAS was firstly described more than 50 years ago (Kinsburn, 1962) [4]. UK scientists point to a morbidity for this pathology of 0.18 per 1 million people per year [6], but there is no general international statistics. International recommendations include three of the following diagnostic criteria for describing the typical

syndrome: opsoclonus, myoclonus/ataxia, behavioral changes/sleep disorder and neuroblastoma [2].

In addition, there are almost always sleeping disorder, cognitive dysfunctions and behavioral disorders, increased sensitivity to acoustic sensory stimuli and associated anxiety [1,3]. The age of the beginning is about 3 years. This disease is more likely to be found in children, but in adults it can also be detected as paraneoplastic syndrome. In 50% of the children, the cause of OMAS is a parainfectious process, the rest of the 50% of children have an association with neuroblastoma (ganglioneuroblastoma or ganglioneuroma), but only from 2% to 3% of children with neuroblastoma have OMAS [8].

The ***purpose*** of the research — to present a case of the rare Kinsburn's Encephalopathy — OMAS and to attract the attention to its timely diagnosis.

Clinical case

A *girl S.*, 2014 year of birth was admitted to the neurology department of NCSH «OKHMATDYT» in May 2016 with a diagnosis of neurodegenerative central nervous system (CNS) disease with complaints of «running» eyes, violations of walking — an expressed swing and loss of self-procession. It is known from the anamnesis that at the end of 2015 she received a vaccine against poliomyelitis (OPV vaccine). Being absolutely healthy after 3 weeks, the generalized symptoms of acute respiratory infections were noted during 3–5 days of light severity, and in February 2016, the parents noticed disturbances of the movement (a child began to wamble, often fell), changes in the eyes movement (eyes began to «run» from side to side, including the sleeping period) and tremor appeared more in the right hand and head (significantly increased with excitement). Parents were also alarmed by the expressed emotional changes: roaming, anxiety, aggression, and hysterics during every day, which had never been before. The brain's Magnetic Resonance Imaging (MRI) (27.03.16): without pathology (hypoplasia of the right vertebral artery is a variant of the norm).

In the diagnosis, a careful description of the neurological status is important, as the rude horizontal nystagmus (which was described earlier), the gross coarse tremor of the extremities, the head (especially during agitation) is a myoclonic hyperkinesis of the oculomotor muscles; low-amplitude myoclonia of the trunk muscles and extremities that resemble a generalized tremor. During the first three days, a true diagnosis was made: Kinsburn's Encephalopathy — opsoclonus-myoclonus syndrome, and the search for the cause of the autoimmune process began. Immunocytological examination of subpopulations of peripheral blood lymphocytes (cellular immunity), determination of the level of immunoglobulins (humoral link) and autoantibodies to neuroantigens (increasing level of antibodies to neuronspecific enolase) was provided. When the chest X-ray was provided, an additional shadow on the background of the heart shadow was detected.

Computer tomography (CT) of the chest and abdomen was provided. Examination was performed on a multi-spin CT scanner Siemens Somatom Definition AS. The scanning was performed on a protocol with automatically selected values of kV and mAs, the thickness of the cut is 1.5 mm. Equivalent exposure dose — 2.45 mSv. An intravenous bolus amplification was performed using a nonionic, iodine-containing contrast agent Tomohexol 350 at a rate of 1 ml/kg body weight.

Immunocytological study of subpopulations of peripheral blood lymphocytes: the total content of lymphocytes is slightly increased due to the content of T lymphocytes without altering the CD4 + / CD8 + ratio. The content of B-lymphocytes is within the age limit. Expression of HLA-DR antigen in monocytes is moderately reduced (Table 1).

In the CT scan series — scans in the posterior mediastinum on the left, paravertebral at the level of 5–9 thoracic vertebrae, there is a tumor mass of the irregular, spindle-shaped form that is in contact with the wall of the aorta and the lower lung vein, 6th segment of the left lung, as well as with the spread in the posterior sections 6 and 7 of the intercostal space, merging with intercostal nerves. Maximum dimensions of the mass in the vertical direction are 54 mm, thickness (saggital size) up to 19 mm, paravertebral lateral size is about 21 mm and at the 6th intercostal level is up to 36 mm. The structure of the formation is soft-tissue, with uneven, rather intensive accumulation of contrast, in the upper sections of the formation there are small calcifications. The contours are clear enough, except of the back surface, in the area of merging with the affected areas of the intercostal nerves (Fig.).

In addition to the diagnosis, the child immediately began to receive adequate therapy — intravenous immunoglobulin at a dose of 2 g/kg for a 5-day course. On the background of the

Table 1

Immunocytological study of subpopulations of peripheral blood lymphocytes

Indicators	Values			
	%	Normal range, % (1–6 years)	Absolute count, 10^9/l	Normal range, 10^9/l (1–6 years)
Lymphocytes	47	38–53	**5.687**	2.9–5.1
B-lymphocytes (CD 19+/CD20+)	17.0	21–28	0.97	0.7–1.3
B-lymphocytes (CD20+/CD5+)	3.5	Not more than 30% from all B-lymph	0.2	0.25–0.27
T-lymphocytes(CD3+)	71	62–69	**4.04**	1.8–3.0
T-helper (CD3+/CD4+)	34.3	30–40	**1.95**	1.0–1.8
T-suppressors /cytotoxic (CD3+/CD8+)	31.3	25–32	**1.78**	0.8–1.5
Natural killers (CD16/56+/3-)	11.0	8–15	**0.63**	0.2–0.6

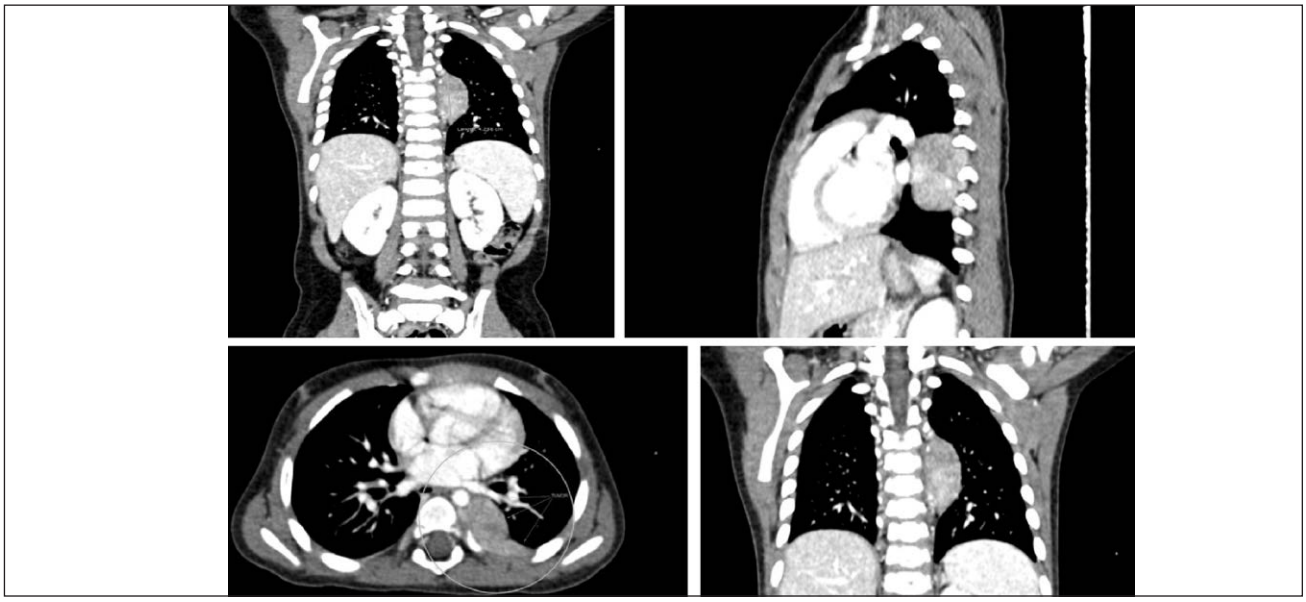

Fig. CT of the chest and abdomen

Table 2

Immunohistochemical studies

Marker	Reaction evaluation
Monoclonal Mouse Anti-Human **Neuron Specifie Enolase** Clone BBS/NC/V1-H14	+ focal
Monoclonal Mouse Anti-**Vimentin**, Clone Vim 3B4 (Daco M7020)	+ in the stroma of the tumor - in the tumor cells
Monoclonal Mouse Anti-**Synaptophysin**, Clone SY38 (Daco IR776)	+ focal
Polyclonal Rabbit Anti-Human **Chromogranin A** (Daco IR502)	+

Table 3

Autoantibodies to neuroantigens after removal of neuroblastoma (Serum 27.10.17)

Indicator	Values (normal range)
Autoantibodies to the general human brain antigen	**40.5** (29.00±1.50)
Autoantibodies to the main protein (ELISA)	**44.0** (26.05±1.50)
Autoantibodies to S-100 protein	**14.2** (12.60±0.25)
Autoantibodies to neurospecific enolase	**32.7** (23.10±0.35)

received therapy, the positive dynamics was marked, she began to walk independently, the atactic syndrome decreased, and the opsoclonus remained unchanged. In general, patient received 6 courses Intravenous immunoglobulin (IVIG) for 1 year.

Therefore, the main cause of autoimmune defeat of the nervous system was revealed and the child was directed to the further examination and treatment at the Cancer Institute of the National Academy of Medical Sciences of Ukraine. Based on the results of morphological and immunohistochemical studies in the operation material, the resulting phenotype is characteristic of neuroblastoma (ICD-O code 9500/3) (Table 2, 3). A radical deletion of the left hemotouractic neuroblastoma was performed:

pT1bpN0M0, N negative form. For the diagnosis of catecholamine-producing tumors, a urine test (including vanillylmandelic and gamavanillic acid) was done — the indicators are within normal limits.

Discussion

Ataxia is usually the first manifestation and progresses until a child can no longer walk or stand. Since this is the initial sign, it often leads to the diagnosis of acute post-infectious cerebellar ataxia. From 70% to 80% of cases may have neurological consequences: cognitive deficits, visual, motor, practical, language and behavioral disorders. In some cases, the appearance of cerebellar atrophy in the long term has also been described. Currently, the study of the neuropsychological development of these patients is essential, since they are very irritable, demonstrate serious learning disabilities and can develop mental retardation [7], which can distract from the timely establishment of an accurate diagnosis and direct the doctor to the wrong diagnosing path and, most importantly, to waste time when there is a need for surgery and immunosuppression.

Ataxia and the key symptom of opsoclonus — myoclonus in 50% of cases occurs as a manifestation of the tumor process, in particular neuroblastoma, the remaining 50% of cases occur as a parainfectious process against the background of a viral infection more often — Epstein–Barr Citomegalovirus — *Hepatitis virus*, *Borreliosis*, *Mycoplasma pneumoniae* — virus *Herpes* type 6, Varicela zoster, *Streptococcus* [10] and constantly needs differential diagnosis with acute post-infectious cerebellar ataxia, which, unlike the opsoclonus-myoclonus syndrome, occurs 1–2 weeks after a diagnosed viral infection and disappears without a trace after 3–6 months. Paraneoplastic OMAS requires rapid diagnosis, which affects the quality of treatment and the patient's future life.

Recent publications point to other possible localizations of this tumor, not only in the mediastinum [9]. Therefore, the authors, who present these cases, point to the need for the whole-body MRI. Observation of a group of children in 2019 showed that children with a neoplastic process and OMAS had an earlier onset (on average 15.5 versus 26.3 months) and rapid development, as well as a direct correlation with the morbidity and prognosis [9]. Whole-body MRI is a safe and effective examination method and should be considered in pediatric cases of OMAS due to the paraneoplastic nature of the disease with associated tumor, high sensitivity of disease detection, absence of ionizing radiation, excellent tissue resolution, and demonstrated efficacy in pediatric imaging.

Since OMAS is very rare, a paraneoplastic process must be constantly suspected and considered among the differential diagnoses of acute and subacute ataxias in children. Immunosuppressive treatment with early onset improves the long-term prognosis of OMAS, and surgical resection of neuroblastoma temporarily improves symptoms, although they usually do not completely disappear until immunosuppressive treatment is started. Currently, standard treatment includes corticosteroids or adrenocorticotropic hormone (ACTH) continuously. Symptomatic treatment usually results in clinical improvement in about 2 weeks in 80% of cases. Literature studies show that the response with ACTH appears to be more effective than with steroids. Currently, some authors recommend early addition of Rituximab to the therapeutic regimen in those cases [5].

Long-term follow-up of our presented patient shows a typical case of OMAS, a correct, rapid diagnosis and adequate treatment. However, it is also typical that the child has not been in stable remission for 3 years and has neurocognitive and psychological problems in behavioral disorders. It should also be noted that the child received many courses of immunoglobulin followed by a temporary improvement, but did not receive other immunosuppressants. Also in the plans there is the possibility of using Rituximab.

Conclusions

This case shows a timely diagnosis of the neoplastic process — neuroblastoma, with the occurrence of pathognomonic syndrome opsoclonus-myoclonus or Kinsburn's encephalopathy. It should be noted that this episode is really rare, but in the neurological department of the National Children's Specialized Hospital «OKHMATDYT» there were 4 children with this disease. Two of them were diagnosed with neuroblastoma, and in the other two cases genesis of the disease was parainfectious.

No conflict of interests was declared by the authors.

REFERENCES/ЛІТЕРАТУРА

1. Bravo J, López–Almaraz R, Mateos M. (2016, Mar 16). Neuropsychological profile in opsoclonus-myoclonus-ataxia syndrome presenting as neuroblastic tumours. Rev Neurol. 62(6): 249–257.
2. De Grandis E, Parodi S, Conte M. (2009). Long-term follow-up of neuroblastoma-associated opsoclonus-myoclonus-ataxia syndrome. Neuropediatrics. 40: 103–111.
3. Green D, Lim M, Lang B et al. (2016, Jul). Sensory Processing Difficulties in Opsoclonus-Myoclonus Syndrome: A Pilot Project of Presentation and Possible Prevalence. J Child Neurol. 31(8): 965–970.
4. Kinsbourne M. (1962). Myoclonic encephalopathy of infancy. J Neurol Neurosurg Psychiatr. 25: 271e6.
5. Ma GM, Chow JS, Taylor GA. (2019, Apr). Review of paraneoplastic syndromes in children. Pediatr Radiol. 49(4): 534–550.
6. Pang KK, de Sousa C, Lang B, Pike MG. (2010). A prospective study of the presentation and management of dancing eye syndrome/opsoclonus-myoclonus syndrome in the United Kingdom. Eur J Paediatr Neurol. 14: 156–161.
7. Park C, Aljabban I, Fanburg–Smith JC. (2019, Dec 19). Pediatric whole body MRI detects causative ovarian teratoma in opsoclonus myoclonus syndrome. Radiol Case Rep. 15(3): 204–209.
8. Rudnick E, Khakoo Y, Antunes NL. (2001, Jun). Opsoclonus-myoclonus-ataxia syndrome in neuroblastoma: clinical outcome and antineuronal antibodies-a report from the Children's Cancer Group Study. Med Pediatr Oncol. 36(6): 612–622.
9. Storz C, Bares R, Ebinger M. (2019, Aug 20). Diagnostic value of whole-body MRI in Opsoclonus-myoclonus syndrome: a clinical case series (3 case reports). BMC Med Imaging. 19(1): 70.
10. Urman G, Leivi M, Chamorro N et al. (2019). Opsoclonus myoclonus syndrome secondary to abdominal neuroblastoma. Presentation of a pediatric clinical case. Arch Argent Pediatr. 117(6): 651–654.

Відомості про авторів:
Стеценко Тетяна Іванівна — к.мед.н., доц., лікар-невролог дитячий Центру стимуляції мозку. Адреса: м. Київ, вул. В. Порика, 13Б.
https://orcid.org/0000-0002-9490-3782.
Федушка Галина Михайлівна — лікар-невролог дитячий відділення неврології НДСЛ «ОХМАТДИТ». Адреса: м. Київ, вул. В. Чорновола, 28/1.
https://orcid.org/0000-0003-1194-6160.
Ребенков Станіслав Олегович — зав. відділенням променевої діагностики НДСЛ «ОХМАТДИТ». Адреса: м. Київ, вул. В. Чорновола, 28/1.
Іванова Тетяна Павлівна — медичний директор НДСЛ «ОХМАТДИТ». Адреса: м. Київ, вул. В. Чорновола, 28/1.
Стаття надійшла до редакції 05.12.2023 р., прийнята до друку 12.02.2024 р.