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Original article

Incidence of Kinsbourne syndrome in patients diagnosed with neuroblastic tumors: a single-center experience and review of literature

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Abstract

Kinsbourne syndrome or opsoclonus-myoclonus syndrome (OMS), also called dancing feet syndrome, manifests in opsoclonus, myoclonus, and ataxia. It occurs more frequently in pediatric patients, and around 50% of cases are caused by neuroblastoma (NBL). This investigation aimed to determine the incidence of OMS in children diagnosed with neuroblastic tumors. Data collected from 2004 to 2019 at the Department of Pediatric Oncology, Hematology, and Transplantology of Poznań University of Medical Sciences (Poznań, Poland) were analyzed. The research group included 119 patients under 18 years of age. There were only 3 cases (2.52%) of OMS in the research group, all younger than 3 years. The tumor was localized in the adrenal gland in 1 patient and paravertebrally in the other 2. The presented symptoms included nystagmus, balance disturbances, and tremors. All cases of OMS in children require imaging to determine whether it is caused by NBL. However, among patients with NBL, OMS is a rare manifestation.

Keywords

Neuroblastoma, opsoclonus, myoclonus, ataxia, Kinsbourne syndrome.

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Introduction

Kinsbourne syndrome, also called opsoclonus-myoclonus syndrome (OMS), was first described in 1962 and manifests in opsoclonus, myoclonus, and ataxia [1]. It also provokes irritability and learning and behavioral disturbances in children. Of the prodromal symptoms of OMS, irritability is the most frequent manifestation, observed in more than 60% of patients. Furthermore, OMS can be preceded by crying, vomiting, nausea, fever, coughing, or other nonspecific symptoms [2]. OMS occurs more frequently in pediatric patients, with an estimated incidence of 0.27-0.4 cases per million children, according to Japanese research [3]. Around 50% of cases are caused by neuroblastoma (NBL). However, OMS can also occur as a result of infection [2, 4]. The pathogenesis is considered to be immune-mediated [2].

NBL is a small blue round cell tumor in histopathology. These tumors most commonly occur in the first 12 months of life and are localized in the abdomen, especially the adrenal medulla. The International Staging System defines 4 stages. The stages 1, 2, and 4S describe patients with localized tumors, which should be operated firstly. These patients have a good prognosis. In the group of patients with stage 4S NBL, children are younger than 12 months old and metastases are generally limited to the liver, skin, and bone marrow, which may disappear after removal of the first NBL focus. The current investigation aimed to determine the incidence of OMS in children diagnosed with neuroblastic disease.

Materials and methods

Data collected from 2004 to 2019 at the Department of Pediatric Oncology, Hematology, and Transplantology of Poznań University of Medical Sciences (Poznań, Poland) were analyzed. The research group included 119 patients diagnosed with a neuroblastic tumor. Specifically, there were 107 children with NBL, 10 with ganglioneuroblastoma, and 2 with ganglioneuroma. The inclusion criteria were patients aged under 18 years on the day of diagnosis and diagnosis of a neuroblastic change confirmed by imaging examination. The exclusion criteria were other neoplastic or chronic diseases. The patients included in the research group had an average age of 2.2 years old. Of the patients, 41.18% were younger than 1 year old, 48.74% were between 1 and 5 years old, and only 10.08% were older than 5 years. The group was composed of 62 girls and 57 boys. The diagnostic criteria of OMS were symptoms of ataxia, myoclonus, opsoclonus, or behavioral and sleep disturbances.

Results

There were only 3 cases of OMS in the research group. Two of them were associated with NBL, and 1 with ganglioneuroblastoma. The incidence of OMS in this analysis was equal to 2.52% of the whole group and 1.87% among children with NBL. The 3 children with OMS were aged 15 months, 17 months, and 3 years. According to that, OMS was present in 5.17% of patients from 1 to 5 years old. One of them had NBL localized in the adrenal gland, while the tumor was localized paravertebrally in the other 2 patients. OMS occurred in 2.04% of patients with adrenal gland localization of the tumor. All of the patients had horizontal nystagmus, 2 had balance disturbances, and 2 suffered from tremors.

In the whole group, the most frequent localization was the adrenal gland (50%), with the right gland about 2 times more commonly affected than the left one. NBL was not localized in the abdomen in about 25.5% of cases, with the mediastinum being the most frequent location.

Three case reports

The first patient was a 15-month-old boy. He presented to the clinic with an unstable walk, balance disturbance, and falls, in addition to vomiting in the mornings starting 2 weeks prior. Neurologic examinations did not detect any deficits or reflexes abnormalities. However, rotary nystagmus, extremities and muscles tremor, straight leg positioning, and balance disturbances were observed. He had influenza. The MRI examination showed a tumor localized paravertebrally in the abdomen.

Ganglioneuroblastoma diagnosis in stage 2B of malignancy was confirmed. During chemotherapy treatment, he suffered from a few infections. The continuing problems with opsoclonus and myoclonus caused delayed walking. The child underwent abdominal surgery and 12 cycles of cyclophosphamide and dexamethasone. Cycles of plasmapheresis and immunoglobulin transfusion were also performed as part of the treatment. The last MRI did not detect any abnormalities, and the patient's ganglioneuroblastoma has stayed in remission for the past few years.

The next patient was a 3-year-old girl with balance disturbances, resting tremor, and opsoclonus. During hospitalization, she presented symptoms of an infection (fever, rhinitis) with a seizure, which resulted in antibiotic therapy. Computed tomography showed a mass of 3.5 × 2 cm in the right adrenal. NBL in stage 1 of malignancy was diagnosed. The girl underwent radical surgery. In the neurologic examination, she presented with horizontal opsoclonus, positive Romberg's test, and normal reflexes, without meningeal or focal signs. The patient achieved remission of NBL.

The last patient was a 17-month-old girl who presented with horizontal opsoclonus and irritability. She suffered from recurrent tremors of the upper extremities and trunk. Magnetic resonance showed a paravertebrally localized mass of 4.9 × 3.4 × 2.7 cm adjacent to the aorta, renal vessels, left kidney, and ureter (**Fig. 1** and **Fig. 2**). The malignancy features were observed after contrast admission. The patient was transferred to the Surgery Department to undergo an operation. The tumor was radically removed from the peritoneal incision. No enlarged lymph nodes were found. Histopathological examination results in poor differentiated NBL diagnosis. Unfortunately, the surgery was not radical. No follow-up information was accessible.

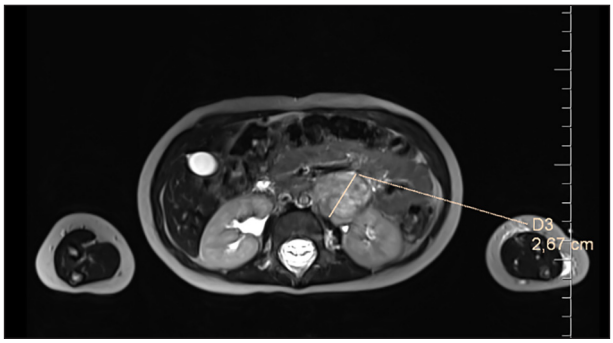

Figure 1. The tumor localized paravertebrally on the left side.

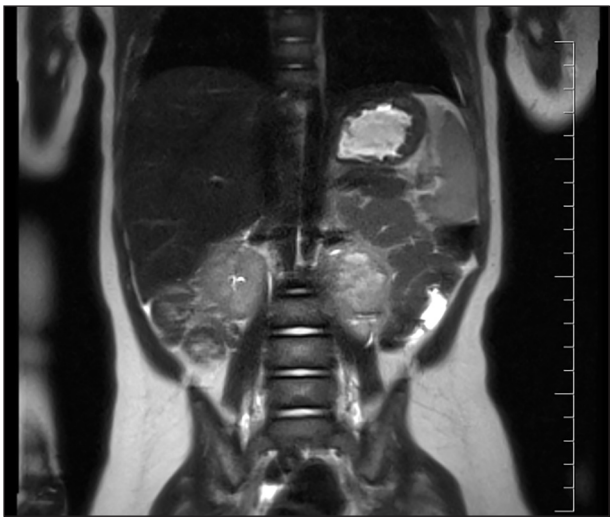

Figure 2. Neuroblastoma (NBL) in the paravertebral localization.

Discussion

The OMS incidence in patients with NBL was equal to 1.87%, which is comparable to other studies [5]. The adrenal medulla is the most frequent localization of NBL, and a palpable mass in the abdomen is one of the most common symptoms. However, NBL can also manifest in other neurological symptoms, similar to Horner syndrome [6, 7]. According to the authors' knowledge, very few studies have focused on OMS incidence among patients with neuroblastic disease.

The most frequent cause of OMS in children is NBL [8, 9]. In adults, the paraneoplastic etiology is also very common, especially in patients with breast cancer and small cell lung cancer [10-12]. In patients admitted with opsoclonus and ataxia, it is essential to ask the patient about previous infections as a parainfectious syndrome is also common. Infections associated with OMS include the following: rubella meningoencephalitis, rotavirus enteritis, influenza A, mumps, human herpesvirus 6, varicella zoster, malaria, *Streptococci*, coxsackie, Epstein-Barr, West Nile, chikungunya, and dengue virus [10, 13-15]. The patient should also be tested for HIV, especially in suspicious or unclear cases, as there are many reports of a relationship between HIV and OMS [16, 17]. Furthermore, there are many cases of pharmacologically induced OMS, for example, caused by neurotoxic cefepime or long-term cyclosporine use [18, 19].

A study performed by Brunklaus et al., including 101 patients with OMS (age range from 3 months to 8.9 years), reported that 90% of these children presented before 3 years old. These data were collected over 56 years. In this paper, 56 children

with symptoms of an infection or with an infection in their recent medical history were described, and 11 of them had NBL [9]. In these 11 cases, the real etiology of OMS was unclear, highlighting the challenges associated with identifying the cause of OMS [9]. In our study, 2 of the 3 patients had an infection during their first hospitalization, which occurred following the manifestation of the first symptoms of OMS. Therefore, we do not believe that these infections were correlated with OMS.

Muthusamy et al. described 22 cases of OMS in children. A tumor was detected in 11 patients (50%), and all of these children had NBL. The mean onset of symptoms was at 1.74 years of age [4], which is comparable with Japanese population studies with the median age of 16.5 months [3]. OMS occurs slightly more frequently in girls than in boys. They also observed that an earlier diagnosis and surgery treatment provides better results in terms of remission. However, in the cohort, tumor removal was not enough to achieve remission of the neurological symptoms [4]. Also, in our research, surgery did not result in OMS remission.

Another analysis of the causes of OMS was performed by Pranzatelli et al. on cases in the United States. The study group consisted of 356 children aged from 0 to 10 years, but most children in the group were younger than 3 years old. Of the study group, 50% of patients had a neuroblastic tumor. Among the NBL cases, 93% were classified as stage 1 or 2. In the majority of patients, NBL had an adrenal or abdominal/paraspinal localization [2, 8].

Hasegawa et al. described 23 children with OMS based on a retrospective analysis of Japanese pediatric patients. NBL occurred in 10 patients, 9 had an infection, and in 2, the recent vaccination was described [3].

Garg et al. reviewed all Indian case reports in which patients ranged in age from 11 months to 60 years. A tumor (especially NBL) was the most frequent cause, but parainfectious etiology was also quite common [10].

The tumor etiology differs between the papers. Still, an incidence of around 50% is the most frequent result. In 92% of tumor etiology cases in pediatric patients, the diagnosis is NBL or ganglioneuroblastoma [2-4, 9, 10].

Tumor incidence in patients with OMS described in different papers is presented in **Fig. 3**.

The critical point of symptomatology is the regression of developmental motor and cognitive milestones, as well as behavioral problems (fearful actions, anger, or unreasonable crying) and sleep disturbances [20]. Catsman-Berrevoets et al. presented a study describing 8 children with OMS with an average age of 23 months. Four of them had NBL, and in 2, a parainfectious cause was probable. They all were treated with immunomodulation medications. At follow-up, 2 children were still dysarthric, and the improvement in motor function was more significant than the changes in cognitive and behavioral symptoms of OMS [20]. OMS can result in disabilities or delayed psychomotor development, so it is crucial to determine the cause of the symptoms and begin treatment. As part of therapy to decrease the symptoms of OMS, immunomodulation methods such as steroids, adrenocorticotrophic hormone, and intravenous immunoglobulin may be chosen [2, 9].

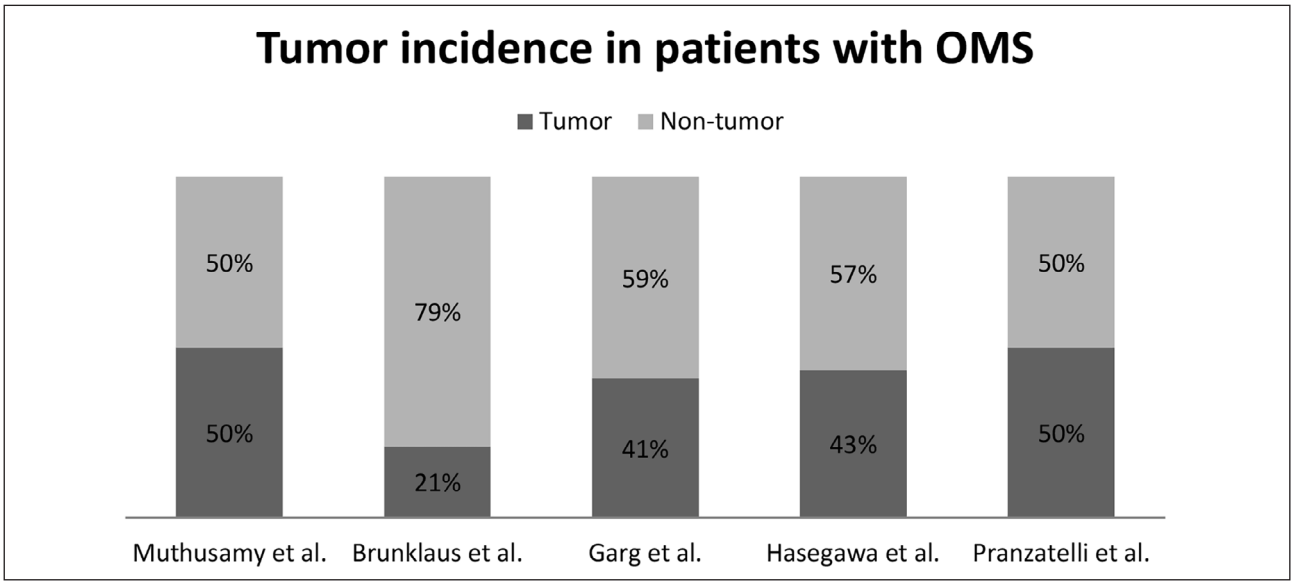

Figure 3. Tumor incidence in patients with opsoclonus-myoclonus syndrome (OMS) described in different papers [3, 4, 8, 9, 10].

The limitations of this study include its retrospective nature and concentration at the Oncology Department, meaning that no follow-up information about the neurologic development of children was available.

Conclusions

Every case of OMS in children requires imaging to determine whether it is caused by NBL. However, among patients with NBL, OMS is a rare manifestation. Nevertheless, OMS symptoms can lead to severe problems, so oncologic and immunomodulation treatment should be appropriately planned.

Data availability statement

The data that support the findings of this study are available from the corresponding author, K.K., upon reasonable request.

Statement of Ethics

This study involved retrospective data analysis, so ethics approval was not required.

Declaration of interest

The Authors declare that they have no competing interests. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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