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Esthesioneuroblastoma in children and adolescent – a systemic review

Estesioneuroblastoma w populacji dziecięcej – przegląd literatury

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Keywords

esthesioneuroblastoma, olfactory neuroblastoma, pediatric skull base surgery, endoscopic skull base surgery, skull base tumor, pediatric neuroendoscopic surgery, head and neck cancer, skull base cancer

Summary

Esthesioneuroblastoma, or olfactory neuroblastoma, is a rare malignant neoplasm of the sinonasal tract originating from the olfactory neuroepithelium. It most often presents in the superior nasal cavity. The etiology of esthesioneuroblastoma is still unknown. The cancer develops asymptomatically for a long time. The most common complaints reported by patients include a feeling of unilateral nasal blockage (70%), nosebleeds (50%), facial pain, visual disturbances, lack or weakness of smell, excessive tearing and neurological symptoms associated with infiltration of structures of the anterior cranial fossa. Endoscopic surgery with or without craniotomy is the first choice treatment. The majority of these patients are also treated with adjuvant chemotherapy or radiation therapy. A comprehensive literature search was performed. We limited results to publication from 2013-2023. In 12 articles a total of 83 patients were evaluated. Age range was 0,6 year to 21 years. The clinical course, symptoms, diagnostics, treatment and outcomes were analyzed.

Słowa kluczowe

estesioneuroblastoma, nerwiak węchowy zarodkowy, operacje podstawy czaszki u dzieci, endoskopia podstawy czaszki, guz podstawy czaszki, pediatryczna operacja podstawy czaszki, rak głowy i szyi, rak podstawy czaszki

Streszczenie

Estesioneuroblastoma, zwana inaczej nerwiakiem węchowym zarodkowym, jest nowotworem złośliwym wywodzącym się z komórek nabłonka węchowego. Etiologia jest nieznana. Nowotwór długo rozwija się bezobjawowo. Guz rośnie ekspansywnie, penetrując do zatok nosowych, jamy nosowej, oczodołu i przedniego dołu czaszki. Do najczęstszych dolegliwości zgłaszanych przez pacjentów należą: uczucie jednostronnej blokady nosa (70%), krwawienia z nosa (50%), ból twarzy, zaburzenia widzenia, brak/osłabienie węchu, nadmierne łzawienie oraz objawy neurologiczne związane z naciekaniem struktur przedniego dołu czaszki. Diagnostyka opiera się na endoskopii jam nosa, badaniach obrazowych (tomografia komputerowa i rezonans magnetyczny) oraz weryfikacji histopatologicznej. Leczenie w zależności od stopnia zaawansowania polega na chirurgicznym usunięciu guza, radioterapii i chemioterapii. Przeprowadzono dogłębną analizę literatury opisującej pacjentów pediatrycznych leczonych z powodu nerwiaka węchowego zarodkowego. Wyniki ograniczyliśmy do publikacji z lat 2013-2023. W 12 artykułach oceniono łącznie 83 pacjentów. Przedział wiekowy wynosił od 0,6 roku do 21 lat. Przeanalizowano przebieg kliniczny, objawy, diagnostykę, leczenie i rokowanie pacjentów z rozpoznaną estesioneuroblastomą.

Introduction

Esthesioneuroblastoma, otherwise known as embryonal olfactory neuroblastoma, is a malignant neoplasm derived from olfactory epithelial cells (neuroectodermal cells). These cells are typically located in the upper part of the nasal cavity, including the superior nasal turbinate, the superior part of the septum, on the roof of the nasal cavity (cribriform plate). The tumor is very rare in the pediatric population with a frequency of < 0.1 per 100,000 (1). It is diagnosed in any age group, however, 2 peaks of incidence are found – the first in young adults up to 20 years of age and the second peak between 50-60 years of age (2). The cancer develops asymptomatically for a long time. The most common complaints reported by patients include a feeling of unilateral nasal blockage (70%), nosebleeds (50%), facial pain, visual disturbances, lack/weakness of smell, excessive tearing and neurological symptoms associated with infiltration of structures of the anterior cranial fossa. Although the tumor originates from the olfactory epithelium, anosmia is a rare symptom occurring in only 5% of patients (1, 3, 4). The tumor grows expansively penetrating into the nasal sinuses, nasal cavity, orbit and anterior cranial fossa and does not differ in appearance from other nasal neoplasms however often endoscopic examination alone does not reveal any proliferative changes (3). Cases of neuroblastoma accompanied by paraneoplastic syndromes in the form of Cushing's syndrome with excessive ACTH levels, malignant hypercalcemia, and hyponatremia caused by excess vasopressin are also described (5-8). Infiltration of anterior cranial fossa and orbital structures is found in 10% of adults and about 50% of children with esthesioneuroblastoma (9). Lymph node metastases are present in 8-10% of patients at the time of diagnosis (10). The primary diagnosis is based on endoscopic examination of the nasal cavities, computed tomography (CT) and magnetic resonance imaging (MRI). The differential diagnosis should consider striated cell sarcoma, diffuse large B-cell lymphomas, Ewing tumor, inverted papilloma, hemangioma, low-differentiated carcinoma, neuroendocrine carcinoma, melanoma and meningioma (11, 12). The disease progresses more aggressively in the pediatric population compared to the adult group. Treatment, depending on the stage, consists of surgical removal of the tumor, radiation therapy and chemotherapy (13).

Material and methods

A comprehensive literature search was performed using the databases of PubMed and The Cochrane Library. Our search terms and medical subject headings (MeSH) were: esthesioneuroblastoma AND child(ren) OR pediatric AND English (language). We limited results to publication from 2013-2023. All articles that addressed the topic were screened by full text review. Inclusion criteria were: cases diagnosed and pathology-confirmed as esthesioneuroblastoma, cases in pediatric population up to 21 years of age, details of cases available and english language of publications. Only manuscripts evaluating pediatric esthesioneuroblastoma exclusively were included to prevent ambiguity of data from series that included both pediatric and adult patients. The remaining articles meeting all inclusion and exclusion criteria were included for qualitative and quantitative analysis.

Results

The initial database query identified 58 articles, with 12 meeting inclusion criteria. In 12 articles (14-25) a total of 83 patients were evaluated. Male group counted 32 boys and female group gathered 51 girls. Male to female ratio was 1:1.59. Age range was 0,6 year to 21 years (tab. 1). All studies were retrospective case series. Nasal obstruction was the most common presenting symptom, followed by headache, epistaxis and visual disturbance. Ophthalmic disorders included visual disturbance, proptosis, diplopia, tearing, decreased visual acuity and blindness. Patients also complained of neck swelling, recurrent sinus infections, allergic symptoms, facial swelling, dizziness, anosmia, nausea, vomiting and seizures. In diagnostic all patients underwent computer tomography (CT) and magnetic resonance imaging (MRI). The extent of oncological process was categorized provide Kadish staging (tab. 2). 2.4% (2/83) of patients were Kadish A, 25.2% (21/83) were Kadish B, 55.4% (46/83) were Kadish C, and 17% (14/83) were Kadish D. Cervical lymph node metastases were found in 17% (14/83) of patients. Histological examination and immunohistochemical analysis of the biopsy confirmed the diagnosis of olfactory neuroblastoma. Most patients received surgery and/or chemotherapy and/or radiation therapy. 47% patients (n = 40) was treated with triple modality therapy (surgery + radiation + chemotherapy). Treatment parameters are summarized in table 3. Chemotherapy included cisplatin, etoposide, doxorubicin, cyclophosphamide, ifosfamid, carboplatin and etoposide. These therapies were based on the chemotherapy protocols set in place at each institution or country. Seventy children received proton therapy with median radiation dose of 50-60 Gray (Gy) and 1 boy was treated with palliative radiotherapy. Surgical resection was performed as endoscopic endonasal resection or craniofacial resection with or without reconstruction. 24% patients died (n = 20). Overall survival rates were 86%.

Discussion

The extensive progression of the cancer at the moment of setting the diagnosis is due to the slow growth of the tumor, the long asymptomatic period and the frequent normal picture of the nasal cavities on endoscopy. At the time of diagnosis, 20.2% of patients are already found to have lymph node metastases (1). Tumors are unilateral, polypoid, soft, grayish-red, well vascularized and covered with unaltered mucosa therefore endoscopic examination of a patient with a tumor may reflect normal (26).

Tab. 1. Demographic characteristics

	N	Age (years)	Male	Female	Kadish stage
Venkatramani et al. 2015 (14)	24	14 (range 0.6-20)	6	18	B-8 C-16
Kababri et al. 2014 (15)	11	14 (range 0.8-18)	3	8	B-5 C-6
Drescher et al. 2024 (16)	15	16 (range: 3-21)	7	8	B-2 C-9 D-4
Lucas et al. 2015 (17)	8	4.6 (range 0.8-9.4)	2	6	B-3 C-1 D-4
Dumont et al. 2020 (18)	18	12.2 (range 0.9-18)	10	8	A-1 B-3 C-10 D-4
Jo et al. 2016 (19)	1	6	1	0	D
Shahriari et al. 2017 (20)	1	1.75	0	1	C
Pacino et al. 2020 (21)	1	16	0	1	C
McDowell et al. 2020 (22)	1	15	0	1	C
Penzhorn et al. 2022 (23)	1	17	1	0	D
Özhan et al. 2023 (24)	1	0.8	1	0	A
Dimassi et al. 2017 (25)	1	13	1	0	C

Tab. 2. Kaddish staging

Kaddish Staging	
A	tumor confined to nasal cavity
B	involvement of one or more paranasal sinuses
C	extension beyond the paranasal sinuses involving cribriform plate, skull base, or orbit
D	regional lymph node or distant metastasis

Tab. 3. Treatment modality

Treatment modality	N
surgery	2
chemotherapy	1
chemotherapy + radiation therapy	6
surgery + radiation therapy	24
surgery + chemotherapy	9
radiation therapy	1
triple modality therapy	40

Esthesioneuroblastoma gives distant metastasis via blood and lymphatic vessels (27). Perineural spread of the tumor has also been described (28). Lymphatic metastasis is most often localized in cervical lymph nodes of group II (90%), I and III (50%) and pharyngeal nodes (40%). Region IV and V are involved in metastasis only in extensive nodal spread (29). Distant metastases are found in the lungs, liver, bones, marrow and meninges (30). Highly differentiated tumors are associated with a higher likelihood of meningeal metastases, while low-differentiated tumors are more likely to progress with local aggression (31). The classification of tumor progression was first developed by Kaddish. It is based on infiltration of adjacent anatomical structures. Advanced stage A refers to tumor confined to the nasal cavity, stage B to the nasal cavity and paranasal sinuses, and stage C to spread beyond the scope of the nasal cavity and sinuses (32). Morita modified this scale by adding stage D – the presence of nodal or distant metastases (tab. 2) (33). 90% of patients at the time of diagnosis are already at stage B or C cancer according to Kaddish (1).

The primary diagnosis is based on endoscopic examination of the nasal cavities, computer tomography (CT) and magnetic resonance imaging (MRI). CT images of the sinuses show an intranasal unilateral pathological polypoid mass emerging from the olfactory bulb, with possible enlargement of the structures of the olfactory organ system and spreading through the cribriform plate toward the anterior cranial fossa (28). Atypical, ectopic, isolated foci of esthesioneuroblastoma occurring in the sphenoid sinus and maxillary sinus have also been described in the literature (34, 35). Magnetic resonance imaging shows perineural spread of the tumor, infiltration of the meninges and subarachnoid space, and infiltration of intracranial structures. It also allows accurate assessment of orbital structures especially in MRI with the signal attenuation (saturation) technique of adipose tissue (FAT-SAT sequence) (28). Calcifications in the

tumor mass and the co-occurrence of cysts are also typical of these tumors (36). PET-CT can identify the presence of 20% more metastases in the lymph nodes of the neck, which are not visualized on conventional CT (37). Cytogenetic findings show various aberrations of genetic material in tumor tissue. Genetic alterations are more numerous in well-differentiated esthesioneuroblastomas compared to low-differentiated tumors. Deletion of the entire chromosome 11 or deletion within the short arm of chromosome 1 (1p35-36) correlates with poor prognosis. Approximately 20% of tumors have mutations (amplification) of the N-myc protooncogene (MYCN) located on the short arm of chromosome 2 (38, 39). The immunohistochemical profile is characterized by positive staining for synaptophysin, chromogranin, CD56, NSE, NFP and S-100 protein (40). Treatment, depending on the stage, consists of surgical removal of the tumor, radiation therapy and chemotherapy. Endoscopic access surgery provides access to the skull base, orbit, sinuses, and allows surgery of the dura, olfactory nerve, olfactory bulb and even brain tissues. Combined access – endoscopic and external via craniotomy is required in high stages of disease (40, 41). The main adverse effects of surgical treatment include meningitis, cerebrospinal fluid leakage, bleeding in the postoperative period, chronic sinusitis, absence or impaired sense of smell and blindness (42). Radiation therapy is indicated in locally advanced tumors ineligible for radical removal, after non-radical surgical treatment or in cases of recurrence. Complications after radiation therapy can include endocrine and ocular disorders (cataracts, retinal fibrosis, retinopathy) (43). The radiation therapy treatment of the pediatric and young patient population carries a higher risk of second cancers induced by radiation. Radiation therapy causes damage to a single or both DNA strands, and this leads to mutations and developing cancer from the irradiated cell (44). There is a greater predisposition to radiation-induced cancers in the female population (45). In a study by Bonnecaze et al. 36% of stage C patients were treated with surgery with complementary radiotherapy, and patients with stage D advancement were treated with radiochemotherapy (48%). Generalized 10-year survival was achieved by 46-60% of patients (41). Chemotherapy reduces the risk of distant recurrence. The prognosis is serious with recurrence rates as high as 10.3% after surgical treatment, and 5-year survival rates as high as 44-91.1% (1, 46). According to stage, 5-year survival for Kadish A is 80%, for Kadish B – 87.7%, for Kadish C – 77% and for Kadish D – 49.5%. Long-term follow-up of patients is recommended because distant recurrences have been found even 10 years after treatment (47).

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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