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Malignant neoplasms of parameningeal region in children - report from two paediatric centres of oncology

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Summary

Subject: To present the analisis of initial clinical symptoms and difficulties in establishing proper diagnosis.
Material and methods: Data on 32 patients with the diagnosis of parameningeal malignant neoplasms were subjected to a retrospective analysis. The study group consisted of 9 girls and 23 boys, at the age of 2-17. The analysis involved clinical symptoms prior to diagnosis, the response to treatment, possible necessary modifications of therapeutic schemes and treatment outcome in particular histological types of parameningeal malignant neoplasms.
Results: The length of history taking in the whole group ranged from 2 weeks to 24 months. The dominant symptoms were directly associated with the local growth of the tumour and its spread to the regional lymph nodes. The extent of spread of the neoplasm in children with STS was found to be: III° in 14 and IV° in 3 patients. All the children with NHL-B were originally assigned to group B according to LMB and the patients with lymphoepithelioma to III° (2 children) and IVA° (4 children) according to TNM and AJCC. Among the patients with parameningeal malignant neoplasms, 21/32 children demonstrated CR after the complete treatment, including 8/17 with STS and all patients with NHL-B, 4/6 with lymphoepithelioma. Seven patients died: 5 with STS and 2 with lymphoepithelioma. The prognosis of four patients undergoing treatment for STS recurrences is uncertain.
Conclusions: Non-characteristic initial clinical symptoms and signs of parameningeal tumours, often suggestive of an inflammatory process, results in diagnostic difficulties. Since radical resection of parameningeal neoplasms in children is impossible, the prognosis depends on the neoplasm's sensitivity to chemo- and radiotherapy.
Key words: lymphoma, lymphoepithelioma, soft tissue sarcoma, children.

Nowotwory złośliwe okolicy okołooponowej u dzieci - raport z dwóch ośrodków onkologii dziecięcej

Streszczenie

Cel: W pracy analizowano wstępne objawy kliniczne oraz trudności w postawieniu właściwej diagnozy.
Materiał i metody: Retrospektywnej analizie poddano dane dotyczące 32 pacjentów z rozpoznaniem nowotworów złośliwych okolicy okołooponowej. Wśród badanych dzieci było 9 dziewcząt i 23 chłopców w wieku od 2 do 17 lat. Analizie poddano objawy kliniczne występujące przed postawieniem diagnozy, uzyskaną odpowiedź na leczenie, ewentualną konieczność modyfikacji schematów terapeutycznych oraz wyniki leczenia w poszczególnych typach histopatologicznych nowotworów złośliwych okolicy okołooponowej.
Wyniki: Długość wywiadu chorobowego w całej badanej grupie wahała się od 2 tygodni do 24 miesięcy. Dominowały objawy związane bezpośrednio z miejscowym rozrostem guza oraz zajęciem regionalnych węzłów chłonnych. Zaawansowanie nowotworu u dzieci z mięsakami tkanek miękkich oceniono na: III° u 14 i IV° u 3 pacjentów. Wszystkie dzieci z NHL-B pierwotnie zakwalifikowano do grupy B wg programu LMB, zaś pacjentów z nabłoniakiem chłonnym do III° (2 dzieci) i IVA° (4 dzieci) stopnia zaawansowania zgodnie z klasyfikacją TNM i AJCC. Wśród pacjentów z nowotworami złośliwymi okolicy okołooponowej, 21/32 dzieci uzyskało całkowitą remisję po zakończeniu leczenia, w tym 8/17 z mięsakami tkanek miękkich, wszyscy pacjenci z NHL-B i 4/6 z nabłoniakiem chłonnym. Siedmiu pacjentów zmarło: 5 z mięsakami

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tkanek miękkich i 2 z nabłoniakiem chłonnym. Rokowanie u 4 pacjentów z mięsakami tkanek miękkich, którzy obecnie są w trakcie leczenia wznowy jest niepewne.

Wnioski: Niecharakterystyczna wstępna symptomatologia kliniczna guzów okolicy okołooponowej, często sugerująca proces zapalny, jest przyczyną trudności diagnostycznych. Ponieważ radykalna resekcja nowotworów okolicy okołooponowej jest niemożliwa, rokowanie zależy od stopnia wrażliwości na chemio- i radioterapię.

Słowa kluczowe: chłoniak, nabłoniak chłonny, mięsaki tkanek miękkich, dzieci.

Introduction

Parameningeal malignant neoplasms are located in the nasopharyngeal cavity, parapharyngeal region, paranasal sinuses, middle ear and anatomical structures of the cranial basis [1]. The diagnosis of neoplasms located in this region is difficult even for experienced physicians. False or delayed diagnosis results mainly from non-characteristic initial clinical symptoms and signs suggestive of an inflammatory process. Additionally, the physical examination of this region is difficult, especially in the early stages of the disease. In the perimeningeal region, the tumours of various histological structures are likely to develop. The most frequently observed ones are: soft tissue sarcoma (STS), non-Hodgkin malignant lymphoma (NHL) and carcinomas. STSs develop from the primary mesenchymal tissue and are divided into two main histological subgroups: rhabdomyosarcoma (RMS) and non-rhabdomyosarcoma (non-RMS). Such tumours account for 7% of all malignant neoplasms in children and their parameningeal location is found in 35-40% of cases [2,3,4,5,6]. NHLs develop from the B- and T- lymphoid line of the lymphatic system. They constitute about 8% of all neoplasms in children; about 20% of them, mainly NHL-B, are located in the parameningeal region [7,8]. The least common neoplasm which occurs in this region is carcinoma of the nasopharynx, also called lymphoepithelioma. Typically, this kind of neoplasm is diagnosed in adults, only occasionally in older children [1,9]. The management and prognosis in perimeningeal tumours in children mainly depend on their histological type and clinical stage [1]. Therefore, the diagnosis of the neoplasm located in this region should be prompt, and the histopathological evaluation of the tumour tissue and subsequent therapy ought to be conducted at the leading centres of children's oncology.

Material and methods

Data on 32 patients with the diagnosis of parameningeal malignant neoplasms, treated at the Paediatric Department of Haematology and Oncology in Lublin and Gdańsk, were subjected to a retrospective analysis. The population under study consisted of 9 girls and 23 boys, aged 2-17 (mean age 6.3 years). In all patients the diagnosis was based on the histopathological evaluation of the tissue collected from the primary tumour and/or the involved lymph nodes

Table 1. Histopathologic type of tumour in children.

histopathologic type of tumour	N	%
Soft Tissue Sarcomas (STS)	17	53,1
- Group of RMS: Rhabdomyosarcoma	15	46,9
- Group of non-RMS: Leimomyosarcoma, Triton tumour	2	6,2
Non-Hodgkin's B-cell lymphoma (NHL-B)	9	28,1
Lymphoepithelioma	6	18,8

(Table 1). In one girl, NHL-B was concomitant with the ataxia-telangiectasia syndrome; one case of non-differentiated soft tissue sarcoma developed as a secondary neoplasm in the boy treated for retinoblastoma in infancy. The stages of involvement in children with STS and NHL-B were determined the basis of protocols used by the Polish Pediatric Group of Treatment of Solid Tumours (PPGGL) and the Polish Pediatric Group of Treatment of Leukaemias and Lymphomas (PPGLBCh), respectively. In patients with the carcinoma of the nasopharyngeal cavity, the extent of spread of the disease was assessed using TNM and American Joint Committee on Cancer (AJCC) classification. The treatment of STS and NHL-B was carried out according to the current therapeutic protocols of PPGGL and PPGLBCh. The patients with STS were subjected to CWS protocols and those with NHL-B to the LMB protocol. Since no uniform therapeutic protocol is available, the patients with lymphoepithelioma were treated with various management protocols.

The present study analyses initial clinical symptoms and signs decribed difficulties in establishing proper diagnosis. Moreover, the analysis concerned the response to treatment, possible necessary modifications of therapeutic schemes and treatment outcome, in particular the histological types of parameningeal malignant neoplasms.

Results

The length of history taking in the whole group examined ranged from 2 weeks to 24 months (mean 4.5 months). The period from the onset of the first clinical symptoms to the final diagnosis was: 2-24 months in children with STS (mean 5.5 months); 2-10 weeks in patients with NHL-B (mean 4.5 weeks) and 3 weeks-24 months in children with lymphoepithelioma (mean 7 months). The clinical symp-

Table 2. Clinical symptoms in children prior to diagnosis.

clinical symptoms	STS (n=7) N / %	NHL-B (n=9) N / %	Lymphoepithelioma (n=6) N / %
snore	10 / 59	5 / 56	-
breathing through the mouth	8 / 47	3 / 33	1 / 17
epistaxis	9 / 53	-	2 / 33
weight loss	9 / 53	-	2 / 33
lymphadenopathy	5 / 29	-	5 / 83
purulent rhinitis	6 / 35	1 / 11	-
dysphalgia	4 / 24	-	3 / 50
earache	6 / 35	-	1 / 17
hypoacusia	4 / 24	-	2 / 33
lockjaw	5 / 29	-	1 / 17
dyspnoea	3 / 18	3 / 33	-
fever	5 / 29	1 / 11	-
dysopia	3 / 18	-	1 / 17
headache	4 / 24	-	-
peripheral facial nerve paralysis	3 / 18	-	-
nodule of the cheek	2 / 12	1 / 11	-
hoarseness	2 / 12	1 / 11	-
exophthalmos	2 / 12	-	-

toms observed before referring the patients to oncological centers are presented in *Table 2*. The dominant symptoms were directly associated with the local growth of the tumour and its spread to the regional lymph nodes, which was found in patients with STS (5/17, 30%) and in those with lymphoepithelioma (5/6, 83%). The extent of the spread of the neoplasm in children with STS was found to be: III° in 14 and IV° in 3 patients. All the children with NHL-B were originally assigned to group B according to LMB while the patients with lymphoepithelioma to III° (2 children) and IVA° (4 children) according to TNM and AJCC. Good responses to oncological treatment were observed in 16/32 patients. The group included 7/17 (41%) patients with STS (all with the embryonal subtype), 5/9 (56%) with NHL-B, and 4/6 (67%) with lymphoepithelioma. Complete remission (CR) of the neoplastic disease was achieved in those the patients. In the remaining 16 patients, due to insufficient response to treatment or recurrences, the therapeutic protocols had to be modified to more aggressive treatment of the line II. Among the STS patients the lack of any response to chemotherapy was observed in three cases; two of them died of the disease progression and one with the alveolar type of RMS of the therapy-induced complications. Local recurrences of the neoplastic process occurred in 7 (41%) children with STS. This group included patients who completed the line I protocol of treatment as well as those not subjected to surgical procedures. Two patients of this group died due to neoplasm progression, four children are undergoing treatment for STS recurrences, and in one patient CR was achieved. Two children with NHL-B were shifted from group B to C due to insufficient response to chemotherapy. Local recurrences developed in two children, including the patient with the ataxia-telangiectasia syndrome. In both cases a recurrence programme was used, which resulted in CR. One patient was subjected to autologous bone marrow transplantation (auto-BMT). The recurrences were observed in two patients with lymphoepithelioma. In both of them metastases developed, those to the lymph nodes of the mediastinum and lungs.

At present, among the patients with perimeningeal malignant neoplasms, 21/32 (66%) children demonstrate CR after complete treatment, including 8/17 (47%) with STS, all patients with NHL-B and 4/6 (67%) with lymphoepithelioma. The observation period ranged from 12 months to 9 years (mean 5.3 years). Seven patients died: five with STS and two with lymphoepithelioma. In the majority of these cases the cause of death was progression of the neoplastic disease, one child with STS died of treatment-related complications. The prognosis of four patients undergoing treatment for STS recurrences is indefinite.

Discussion

Despite enormous advances in the treatment of neoplasms in children, malignant neoplasms located in the perimeningeal region still pose problems for general practitio-

nersas well as for children's oncologists. An early diagnosis of the neoplasm in this region is not easy [1,9]. The symptoms of the local growth of the tumour such as: snoring, mouth breathing, epistaxis, chronic rhinitis are non-characteristic and may be suggestive of an inflammatory process. In the group of patients analysed by us, all clinical symptoms reported by children were interpreted by general practitioners as the symptoms of upper respiratory tract infections. The lack of effects of antibacterial treatment and deterioration of the general condition of patients resulted in additional diagnostic procedures: X-ray pictures and tissue biopsies for histopathological examinations. Another problem is the interpretation of enlarged lymph nodes of the neck. This symptom was found in 5 of 17 patients with STS and in the majority (5/6, 83%) of children with lymphoepithelioma. It is extremely interesting that this symptom did not arouse oncological vigilance of GPs in any child with NHL-B although enlarged lymph nodes of the neck (hard, painless) were observed in more than a half of patients (5/9) on admission to the oncological hospital and physical examination. The initial clinical symptoms and signs of perimeningeal neoplasms, irrespective of their histological type, was similar. The element differentiating particular groups of patients was the length of history taking. The longest period from the onset of the first clinical symptoms to the final diagnosis (mean 7 months) was observed in the patients with lymphoepithelioma, the shortest one (mean 4.5 weeks) in the NHL-B children. At the moment of diagnosis, in the majority of patients the regional neoplastic process was substantially advanced. The precise assessment of the extent of spread to the perimeningeal structures is widely based on CT and MRI [1,3,10]. CT is particularly helpful in demonstrating the infiltration of the cranial basis bones, in evaluating lymph nodes of the neck and their relation to the surrounding structures, whereas MRI is a useful tool to visualize the paranasal sinuses and to detect the spread of the neoplasm into the cranium [1,10]. The diagnostic procedures of malignant tumours located in the perimeningeal region cannot be confined only to imaging of this region. They should be include ultrasound and X-ray evaluation of the chest and abdominal cavity [1,3]. In our material, initial diagnostic evaluation revealed remote metastatic foci in the liver in two children with STS. Additionally, the initial diagnostic procedures in patients with STS and NHL-B ought to consider the collection of the cerebral spin fluid and aspiration biopsy or trephinobiopsy of the bone marrow [1,3,8]. The initial involvement of CNS was found in three patients while bone marrow infiltration in two children. The final diagnosis of the histological type of perimeningeal neoplasms must be based on morphological and immunohistochemical assessment of the tumour tissue. Combined therapeutic procedures should be conducted at specialized clinical centres. It is impossible to perform radical surgery of parameningeal tumours, therefore a combined treatment, including chemo- and/or radiotherapy, is extremely important. The effectiveness of these methods depends mostly on the histological structure of neoplasms, their biology and sensitivity to chemo- and radiotherapy. The best prognosis is associated with non-Hodgkin lymphomas characterized by high chemosensitivity [11]. In NHL patients, surgery and radiotherapy do not play an important therapeutic role, while the use of systemic chemotherapy brings about 70-80% of CR. In our group of children with NHL-B of the nasopharynx, all the patients achieved CR, including two cases after local recurrence treatment. There are no uniform treatment protocols for children with lymphoepithelioma. In these patients, radiotherapy combined with chemotherapy was found to be highly effective [9]. In the group examined, 4 of 6 patients achieved remission. Two patients developed recurrences and died. The treatment of recurrences remains a serious therapeutic problem. The worst prognosis in patients with parameningeal neoplasms is associated with STS. Radical local treatment, mainly surgical, is the basic element of therapy. The lack of possibilities to perform radical resection of perimeningeal STS significantly decreases the chances of complete recovery. Complementary treatment, such as local radiotherapy and chemotherapy may lead to remission in some patients, particularly in those with tumours highly sensitive to chemo- and radiotherapy, mostly embryonal RMS [13]. The prognosis in alveolar RMS and non- RMS tumours, usually poorly sensitive to systemic treatment, is uncertain. The results of treatment in the STS children analysed in our study confirm these data. Three of 17 patients (18%) showed no reaction to the treatment used, while 7 (41%) had recurrences. Five of 17 patients (29%) died, mainly due to the progression of the neoplasm. The prognosis for 4 children with STS who are being treated for recurrences is highly uncertain.

Conclusions

1. Non-characteristic initial clinical symptoms ang signs of parameningeal tumours, often suggestive of an inflammatory process, cause diagnostic difficulties. Proper diagnosis is usually established in advanced stages of the neoplastic process. Therefore, GPs should have knowledge of early symptoms of perimeningeal neoplasms.
2. Since radical resection of perimeningeal neoplasms in children is impossible, the prognosis depends on the neoplasm's sensitivity to chemo- and radiotherapy. The best prognosis is observed in patients with non-Hodgkin lymphomas; intermediate prognosis is seen in children with lymphoepitheliomas, whereas the worst one in those with soft tissue sarcomas.

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