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CURRENT KNOWLEDGE ON THE EPIDEMIOLOGY, HISTOLOGY, SYMPTOMS, DIAGNOSIS AND TREATMENT OF RHABDOMYOSARCOMA IN THE PAEDIATRIC POPULATION

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ABSTRACT

Introduction and Objective: Rhabdomyosarcoma (RMS) is the third most common solid and extracranial malignant tumour in children. It originates from mesenchymal tissue and is a heterogeneous tumour in terms of location, histology, clinical presentation and prognosis. The aim of this paper is to provide a comprehensive review of the current state of knowledge on this disease.
Description of The State of Knowledge: The total incidence rate of RMS is approximately 4.5 patients per million people under the age of 20. The tumour is most commonly located in the head and neck, less frequently in the urinary tract, limbs and trunk. Histologically, the embryonal type is the most common, accounting for 60-80% of all RMS cases. The symptoms of the disease depend primarily on the location of the primary tumour and may include exophthalmos, visual disturbances, pain and tissue swelling, nosebleeds, haematuria, visible tumours and general symptoms in advanced forms, i.e. weakness, fever and weight loss. One of the key factors influencing the prognosis is the presence of distant cancer metastases.
Summary: The diagnosis of RMS is difficult due to the rare occurrence of the disease and non-specific symptoms. Although the cure rate for local disease is generally > 70% of patients, metastatic disease is still associated with low overall survival despite intensive treatment strategies. Therefore, early diagnosis of the disease is very important for achieving the best possible treatment outcomes and full recovery.

KEYWORDS

Rhabdomyosarcoma, Children, Epidemiology, Diagnosis, Treatment, Prognosis

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Introduction and Objective

Cancers are rare in the paediatric population. However, they pose a serious clinical problem for both doctors and patients and their families, as they are a common cause of death in children. One of the cancers that can occur in this age group is rhabdomyosarcoma (RMS), which originates from primitive mesenchymal cells. Due to the non-specificity of its symptoms and aggressive course, it poses a major diagnostic and therapeutic challenge.

The aim of this article is to provide a comprehensive review of the current state of knowledge on the epidemiology, symptoms, diagnosis, treatment and prognosis of RMS in the paediatric population.

Methodology

The review was based on articles from PubMed and Google Scholar databases. Key search terms included: rhabdomyosarcoma, children, epidemiology, diagnosis, treatment, prognosis. The time frame was selected to ensure a comprehensive analysis of the above topic, using the most recent articles available.

Description of The State of Knowledge

Epidemiology

Rhabdomyosarcoma (RMS) is a highly malignant tumour originating from primitive mesenchymal cells that differentiate into striated skeletal muscle cells. [1,2] RMS is the most common soft tissue sarcoma in children. It is also the third most common solid, extracranial tumour in pre-pubertal children, after Wilms' tumour and neuroblastoma. It accounts for 5-10% of all childhood cancers. [3] In the United States, approximately 350 cases are reported annually. [4] The overall incidence rate of RMS is approximately 4.5 patients per million people under the age of 20. [5]

More than two-thirds of cases are diagnosed in the first decade of life. (Approximately 90% of all RMS cases occur in people under the age of 25, and nearly 70% of patients are children under the age of 10). There are two distinct peaks in RMS incidence: between the ages of 2 and 6 and between the ages of 10 and 18. Rhabdomyosarcoma is slightly more common in male children and in Caucasians. [6]

Most cases occur sporadically. The factors predisposing to the development of this cancer are not fully understood. An increased incidence of soft tissue sarcomas can be observed in genetic syndromes such as: Li-Fraumeni syndrome (associated with a mutation in the TP53 gene, the main tumour suppressor gene), Gardner's syndrome (mutation in the APC tumour suppressor gene), type I neurofibromatosis (deletions in the NF1 gene), Beckwith-Wiedemann syndrome, and Costello syndrome (mutation in the HRAS gene). [3,5,7] Certain environmental factors may also predispose a child to developing RMS, including: intrauterine exposure to X-rays, parental drug use. [7]

RMS can occur in any soft tissue in the body. It is most commonly located in the head and neck area (35-45%), followed by the genitourinary system (20-25%) and the limbs (15-20%). [3]

Histology

RMSs are a histologically diverse group. The World Health Organisation (WHO) has classified RMSs based on histological and molecular characteristics, distinguishing the following types:

- Embryonal rhabdomyosarcoma
- botryoides variant
- anaplastic variant
- Alveolar rhabdomyosarcoma

solid variant,

- anaplastic variant
- Pleomorphic rhabdomyosarcoma
- Spindle cell/sclerosing rhabdomyosarcoma [3]

Embryonal rhabdomyosarcoma (ERMS) accounts for approximately 70% of all paediatric RMS cases. It is the most common form of this cancer in early childhood, especially in children under 10 years of age. [5,6] It is most commonly located in the head and neck region (particularly often involving the orbit [6]) and in the genitourinary system (in the bladder, prostate, vulva/vagina, cervix, soft tissues of the paratesticular viscera and bile ducts). More often than in patients with alveolar rhabdomyosarcoma (ARMS), this group is associated with genetic diseases that predispose to the development of cancer. [d] ERMS has a better prognosis than ARMS, and the granular subtype has a better prognosis than the anaplastic subtype. [8]

The tumour is composed of immature 'rhabdomyoblasts' with poor cytoplasm and round/oval nuclei. The histological picture looks like a combination of stages of striated muscle development occurring in embryonic and foetal development. During rhabdomyoblastic differentiation, primitive oval cells become elongated - referred to as 'tadpole' cells - until they become fully differentiated cells. [3,9] In the granular subtype, there are linear aggregates of tumour cells closely adhering to the epithelial surface. The anaplastic subtype is characterised by enlarged, atypical cells with hyperchromatic nuclei. [8]

Alveolar rhabdomyosarcoma (ARMS) accounts for approximately 20% of all paediatric RMS cases. It is a highly malignant tumour. It can occur at any age, but a higher incidence is observed in older children, adolescents and young adults. It most often develops in the limbs, in the form of a rapidly growing tumour, as well as in the paravertebral region, paranasal sinuses and perineum. It can metastasise to regional lymph nodes. [8] Approximately 80% of tumours morphologically classified as ARMS have a FOXO1 fusion gene (PAX3-FOXO1 or PAX7-FOXO1), while more than 95% of tumours morphologically classified as ERMS do not have FOXO1 fusion. [4] The prognosis for ARMS is often worse due to the presence of these fusion genes, as they disrupt normal cell differentiation.

This tumour is composed of monomorphic primary cells with round, large nuclei, sparse cytoplasm and features of inhibited myogenesis. Numerous small, densely packed cells are separated into distinct clusters by fibrous-vascular septa, resembling alveoli. The alveolar appearance provides high cohesion in the centre of the cluster and less cohesion at the periphery. [8]

Pleomorphic rhabdomyosarcoma rarely occurs in children; it is most commonly detected in adults, often on the limbs. [5] It is characterised by the presence of pleomorphic cells – cells of irregular size and shape. It is associated with a poor prognosis due to its more aggressive clinical course. [10]

Spindle cell/sclerosing rhabdomyosarcoma is also rare in children. It is characterised by spindle-shaped cells and a sclerotic background. Its most common locations are the head and neck, limbs and, of particular note, the perinuclear region in paediatric patients. [10]

Symptoms

The symptoms of RMS in paediatric patients can vary greatly due to the multitude of locations where the tumour can develop. They result primarily from local tumour growth, although they may also be accompanied by general symptoms. This is especially true in advanced stages.

A tumour located in the head and neck (including the nasopharynx, sinuses, middle ear, and parotid space) is characterised by: chronic or acute sinusitis, bloody or purulent discharge from the nose or ear, recurrent obstruction, headache, facial swelling, cranial nerve palsy, proptosis, eye movement disorders and diplopia. [11] A tumour in the orbit typically manifests itself as proptosis, i.e. bulging of the eye, eye movement disorders, visual disturbances or strabismus. In the case of RMS in the urogenital system and abdominal cavity, haematuria, difficulty in urination, abdominal pain and constipation may be observed, and palpable tumour masses may also be present in the vagina or rectum. [5] In addition, changes in the limbs are noticeable,

characterised by a harder, rapidly growing mass in the limbs, swelling, pain when pressure is applied to nerve or vascular structures, and the early appearance of a movable superficial or deep tumour. [12]

RMS growth in the mandible and lung is an unusual location for this tumour. [13,14] Mandibular involvement may be accompanied by swelling, a palpable tumour and facial asymmetry. [13,14] A tumour in the lung may cause coughing, shortness of breath and chest pain. [13,14]

Distant metastases to the lungs, bones and bone marrow, present at the time of diagnosis in approximately 20–30% of patients, may manifest as shortness of breath, bone pain or cytopenias, e.g. infections, anaemia and bleeding. [5,15]

Diagnostics

Imaging tests and biopsy play a key role in the diagnosis of RMS, but recently the importance of tumour markers and molecular diagnostics has been growing.

Magnetic resonance imaging (MRI) remains the basis for imaging in the diagnosis of primary RMS tumours: thanks to its excellent soft tissue contrast, MRI allows for the assessment of tumour size, the degree of infiltration of adjacent structures (muscles, tendons, fascia, canal spaces), contact with vessels and nerves, and the presence of foci of necrosis and bleeding. The standard protocol includes T1-, T2-weighted, T1 contrast-enhanced, and fat-suppressed sequences, and diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps are now routinely added for quantitative assessment of cellularity and response to treatment. MRI is also crucial for planning surgical treatment and radiotherapy. [16] In RMS, quantitative ADC metrics correlate with cellular density and can be used for early assessment of response to chemotherapy — an increase in ADC after treatment suggests cell disintegration/decreased cellularity, while stable/decreasing ADC may indicate disease persistence. However, the accuracy of the method depends on MR parameters, tumour segmentation methods and the presence of necrosis — hence international validation studies emphasise the need to standardise protocols and segmentation quality. [17] There is growing evidence that ADC histogram analyses and morphological/textural features may provide prognostic information and correlate with mutation/fusion status (e.g. FOXO1). In clinical practice, these techniques require standardisation and multicentre validation before widespread implementation. [18] Computed tomography (CT) is mainly a complementary tool in the diagnosis of RMS. It is mainly used to assess possible metastases, especially in the lungs, which are a common site of metastasis for this type of cancer. CT is also used to assess bone lesions, detect calcifications and in situations where MRI is not possible. However, it is worth noting that tests such as PET/CT or PET/MRI can detect metastases with metabolic activity before they become morphologically apparent. [19] Both F-18 FDG PET/CT and PET/MRI are highly sensitive in detecting metabolically active distant metastases and lymph node lesions, and allow for the assessment of tumour metabolic heterogeneity. In selected centres, the use of PET/MRI reduces the number of imaging tests required and provides information on the anatomical structure and location of the tumour as well as its metabolic activity. PET/MRI has particular advantages in paediatric patients due to lower exposure to ionising radiation than PET/CT and better soft tissue imaging. [20]

A biopsy should also be performed to diagnose RMS, which provides material for histopathology, immunohistochemistry, cytogenetic/FISH/RT-PCR and molecular testing. In practice, core needle biopsy is preferred as it provides high sensitivity and specificity and sufficient tissue in most paediatric cases, with less invasiveness than open biopsy. where core needle biopsy is insufficient (e.g. extensive necrosis, difficult access, need for more material), open biopsy is considered. The procedure should be planned by a multidisciplinary team consisting of surgeons, oncologists and radiologists so that the puncture site does not compromise the possibility of resection. [21,22]

Among the immunohistochemical markers that may indicate the presence of RMS, myogenin, MyoD1 (Myogenic Differentiation 1) and desmin are key. A study conducted on a large number of cases showed that both myogenin and MyoD1 have a sensitivity of 97% in the diagnosis of RMS and a specificity of ~90–91%. The concentration of both markers was significantly elevated in the ARMS subtype, which emphasises their diagnostic value. [23] In a study of 119 tumours (including ARMS, ERMS and other tumours), all 69 RMS cases showed negative nuclear staining with myogenin, with ARMS showing positivity in 75–100% of cells and ERMS significantly less (usually <25%). This makes myogenin one of the most reliable markers of myogenic differentiation of tumours. [24] Desmin is a highly sensitive muscle marker, detected in RMS in approximately 89% of paediatric cases — however, its specificity is limited because it is also present in smooth muscles and myofibroblasts, as well as in other tumours. For this reason, it should not be used alone, but in combination with the simultaneous determination of other markers. [25] In molecular diagnostics, FISH

(fluorescent in situ hybridisation) and RT-PCR (reverse-transcription polymerase chain reaction) tests are particularly useful, especially when specific fusions are suspected (e.g. PAX3-FOXO1, PAX7-FOXO1). In the ARMS subtype, the key molecular events are translocations leading to the formation of PAX3-FOXO1 (t(2;13)) and PAX7-FOXO1 (t(1;13)) fusion genes. FISH can be used not only to confirm the fusion status, but also to detect amplification of the FOXO1 locus — this was observed in 93% of PAX7-FOXO1 cases, but only in 9% of PAX3-FOXO1 cases. [26] The RT-PCR method also allows the detection of fusion transcripts in archived paraffin-embedded materials, as confirmed by the available literature — in one of the available studies, all cases with confirmed fusions (both PAX3-FKHR and PAX7-FKHR) were correctly identified, and cases without fusions remained negative. [27]

The diagnosis of RMS in children requires an integrated approach combining histopathological and immunohistochemical assessment, advanced molecular biology methods and comprehensive imaging diagnostics. Imaging tests, primarily magnetic resonance imaging and computed tomography, play a key role in assessing the location of the tumour, its extent, its relationship to critical structures, and the presence of metastases, especially to the lungs or bones. Positron emission tomography using 18F-FDG (PET-CT) can increase the sensitivity of detecting metastatic lesions and is sometimes helpful in monitoring response to treatment. The morphological classification of the tumour, obtained on the basis of a biopsy, is the starting point for diagnosis, but due to the significant similarity of the microscopic image to other sarcomas, it is necessary to use immunohistochemical markers such as desmin, myogenin and MyoD1, which confirm muscle differentiation. Final confirmation of the molecular type of the tumour requires genetic analysis, including detection of characteristic PAX3-FOXO1 or PAX7-FOXO1 fusions in alveolar RMS using FISH and RT-PCR techniques. The integration of imaging, morphological, immunohistochemical and molecular test results not only allows for the precise diagnosis of RMS, but also provides key information for risk stratification and individualisation of treatment in paediatric oncology protocols.

Treatment

The treatment of rhabdomyosarcoma (RMS) is based on a multimodal approach. Treatment decisions depend on many factors, including the location, stage of the tumour, extent of infiltration, lymph node involvement and the presence of distant metastases. [28] Surgical treatment and/or radiotherapy play a key role. Radical removal of the primary tumour, also in the case of neoadjuvant induction chemotherapy, which reduces tumour volume and combats micrometastatic disease, improves prognosis and allows further treatment to be adjusted. It has been found that primary resection has a positive effect even in cases of metastatic disease. [28,29,30] In situations where resection would be associated with functional impairment of the operated site or significant aesthetic impairment, radical radiotherapy is an effective alternative due to the radiosensitivity of rhabdomyosarcoma cells. Optimal results are achieved through complete macroscopic resection supplemented with an appropriately selected dose of radiotherapy, which avoids the need for repeat procedures. [28] Research is currently being conducted on optimising the sequence and timing of surgical interventions and the role of preoperative radiotherapy in order to improve treatment effectiveness and reduce complications.

Chemotherapy for the treatment of rhabdomyosarcoma (RMS) in adolescents and young adults is based on multi-drug regimens, mainly using combinations of drugs such as VAC (vincristine, actinomycin D, cyclophosphamide) commonly used in North America and IVA (ifosfamide, vincristine, actinomycin D) in Europe. [31,32,33] The effectiveness of systemic therapy is high. However, treatment outcomes in young adults are worse than in children, due to both the biology of the tumour (more frequent aggressive subtypes and mutations, e.g. the presence of FOXO1 fusion genes) and physiological factors specific to adolescence that affect the pharmacokinetics and toxicity of drugs. [31] Chemotherapy is associated with side effects, with vincristine-related neuropathies being more common in adolescents, while haematological complications (neutropenia, anaemia) are less common than in children. [33] High doses of alkylating drugs increase the risk of infertility, which is important in the context of the young age of patients. [33] The treatment of RMS requires individualised dosing and the integration of modern diagnostic methods, including genetic testing, with classic chemotherapy and local therapy (surgery, radiotherapy) in order to balance the efficacy and toxicity of the therapy and reduce long-term complications. [31] The long-term side effects of therapy remain a significant challenge – patients treated for RMS have a higher risk of death compared to the general population, even many years after the end of treatment. [32]

In response to these problems, innovative therapeutic methods are being developed, such as immunotherapy, precision drug delivery and gene therapy, which aim to increase the effectiveness of treatment while reducing toxicity and improving patients' quality of life. [32] They are playing an increasingly important

role in the treatment of rhabdomyosarcoma (RMS), especially in advanced cases that are resistant to standard treatment or recurrent. Targeted therapies focus on the molecular mechanisms involved in the pathogenesis of RMS, such as tyrosine kinase receptor signalling pathways (including IGFR1) and mTOR, which influence the proliferation and survival of cancer cells. [33] Molecularly targeted drugs, such as IGFR1 inhibitors, mTOR inhibitors, and other small molecule kinase inhibitors, are being intensively studied as potential agents to improve the effectiveness of therapy. [32,33,34]

Immunotherapy in RMS is based on modulating the body's immune response to cancer cells. Immune checkpoint inhibitors, such as PD-1 and CTLA-4 inhibitors, which can increase T-cell activation against RMS cells, are currently in clinical trials. [24] In addition, adaptive therapies are being developed – TCR and CAR-T therapies, which involve modifying the patient's lymphocytes for more precise recognition and elimination of tumour cells. [33] Although immunotherapy is still an experimental option, it offers hope for improving the prognosis in patients with difficult-to-treat forms of RMS. [32,33,34]

The integration of targeted therapies and immunotherapy with conventional treatment methods offers prospects for more personalised and effective treatment of RMS, although more clinical trials are needed to fully confirm their efficacy and safety. [34]

Prognosis

Children and adolescents with RMS constitute a heterogeneous population with varying overall survival rates, ranging from approximately 6% to 100% depending on defined risk factors. The most important prognostic factors for RMS are: patient age, disease stage (stage and clinical group), FOXO1 gene fusion status, tumour location and the presence of metastases. A poorer prognosis was observed in children aged >10 years and in cases where the tumour size was >5 cm. [4,35,36] No significant differences in DSS (disease-specific survival) and OS (overall survival) were observed between female and male patients. Paediatric patients had significantly better DSS and OS. [37] Locations with a favourable prognosis include the orbit, head and neck (excluding the meninges, sinuses and nose), and the urinary tract (excluding the bladder and prostate). Locations with a poor prognosis include the limbs, retroperitoneal space, bile ducts, meninges, sinuses, nose, bladder and prostate. [4,37]

The presence of FOXO1 fusion is a critical prognostic marker, associated with poorer prognosis and more aggressive disease progression. Patients with ARMS have a poorer prognosis than patients with ERMS. (Approximately 80% of tumours morphologically classified as ARMS have FOXO1 fusion). Mutations in the MYOD1 and TP53 genes are strong negative prognostic factors associated with a very unfavourable course of RMS. [2] Based on clinical and pathological features, a risk group is assigned, which determines the treatment approach. In the treatment of low- and medium-risk RMS, multimodal regimens combining surgery, chemotherapy and radiotherapy are used, resulting in a 5-year survival rate of approximately 70–90%. In advanced, high-risk cases, systemic therapy is based on multi-drug chemotherapy combinations, but despite the intensification of treatment, overall survival remains low, at less than 20%. [4,38]

The introduction of molecular classification and risk assessment (e.g., FOXO1 fusion testing) allows for better tailoring of therapy, enabling milder treatment in patients with a good prognosis and intensification in patients with negative prognostic factors. It is important to conduct further research on molecular biomarkers that will improve the accuracy of prognosis and help in the implementation of targeted therapies.

Summary

RMS is the most common malignant soft tissue tumour in children and the third most common extracranial solid tumour in the paediatric population, after Wilms' tumour and neuroblastoma. RMS originates from mesenchymal cells that have the ability to differentiate into striated muscle. It occurs mainly in children under 10 years of age, with two peaks in incidence: between 2–6 and 10–18 years of age.

This tumour is highly heterogeneous in terms of location (most commonly head and neck, genitourinary system, limbs), histological features (four main subtypes: embryonal – ERMS, alveolar – ARMS, spindle cell and pleomorphic), clinical symptoms and prognosis. The most common histological subtype in children is ERMS (60–80% of cases), which is associated with a better prognosis than the more aggressive ARMS, often correlated with the presence of FOXO1 gene fusion – an important prognostic factor.

The symptoms of RMS are non-specific and depend on the location of the tumour. In the head and neck area, symptoms include exophthalmos, visual disturbances, nosebleeds, neurological symptoms and unilateral facial pain. Changes in the genitourinary system cause haematuria, difficulty urinating, and tumours of the

vagina or anus. Tumours of the limbs manifest as painful swelling or a rapidly growing mass. Due to the non-specific nature of the symptoms and the rarity of the disease, the diagnosis of RMS is often delayed, especially in primary care.

The diagnosis of RMS requires a multi-step approach, including imaging (MRI, CT), biopsy and thorough histopathological analysis using immunohistochemical markers such as MyoD1, myogenin, desmin or vimentin. In addition, molecular diagnostics enable the identification of gene mutations and fusions, which is of significant prognostic and therapeutic importance.

RMS treatment is based on a multimodal strategy – surgery, chemotherapy and radiotherapy. Classic chemotherapy regimens are VAC (vincristine, actinomycin D, cyclophosphamide) used mainly in North America and IVA (ifosfamide, vincristine, actinomycin D) in Europe. In low- and medium-risk RMS, treatment achieves a 5-year overall survival rate of 70–90%. In advanced or metastatic disease, despite intensified treatment, the survival rate falls below 20%.

Modern therapies, such as immunotherapy (e.g. PD-1 inhibitors, CTLA-4 inhibitors, CAR-T therapies) and targeted therapies (IGFR1 inhibitors, mTOR inhibitors), are becoming a promising alternative in resistant or recurrent cases. Early studies indicate their potential to improve prognosis and quality of life for patients, although they are still the subject of intensive clinical research.

The prognosis depends on many factors, such as the patient's age, tumour location, size, presence of metastases, histological subtype and molecular status (e.g. presence of FOXO1 fusion, TP53 mutation, MYOD1). The best prognosis is for tumours located in the orbit and head and neck (outside the meninges), and the worst for tumours in the limbs, retroperitoneal space, sinuses and urogenital system (bladder, prostate).

In summary, despite significant advances in the diagnosis and treatment of RMS, the disease remains both a diagnostic and therapeutic challenge, especially in cases with metastases or unfavourable molecular factors. Early diagnosis, interdisciplinary care and further development of targeted therapies and immunotherapy are of key importance. Raising awareness of this disease among primary care physicians and paediatricians may improve early detection and prognosis.

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