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Langerhans Cell Histiocytosis in Children and Adults: Similarities and Differences

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Abstract

Langerhans cell histiocytosis is an uncommon hematological condition affecting children and adults. It is distinguished by neoplastic infiltration of myeloid dendritic cells and an inflammatory response. Any organ can become dysfunctional as a result of tissue destruction and fibrosis. In almost all cases, activating mutations in the MAPK signal transduction pathway have been found. The earlier these mutations appear during myeloid differentiation, the more severe the disease. The skeleton, skin, and pituitary gland are most typically afflicted in children, but the liver, spleen, and hematopoietic system may also be involved, associated with a worse outcome. In adults, manifestations are most commonly observed in the skeleton, lungs, skin, and in the pituitary region. The course of the disease might range from spontaneous remission to persistent relapse. A histological examination is required to get a definitive diagnosis. In youngsters, where therapeutic surgery and radiation are mostly obsolete, medical therapy is the treatment of choice. Chemotherapy is used when special risk lesions are involved or when children have multifocal skeletal involvement and multisystem disease. In adults, however, local treatments are sufficient in unifocal lesions, and supportive therapy with bisphosphonate is suitable for multifocal bone involvement. Systemic therapy is administered only in patients with multisystem disease and treatment-refractory or quickly reoccurring disease activity. Aside from cytostatics, targeted inhibitors of gene mutations are now accessible for this purpose. While most patients survive, chronic recurrent episodes and late sequelae are the main issues.

Keywords: *Langerhans cell histiocytosis, children, adult patients, similarities, differences.*

Abbreviations: *LCH, Langerhans cell histiocytosis; ICH, indeterminate cell histiocytosis; ECD, Erdheim-Chester disease; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinases; SS, single system disease; MS, multisystem disease; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.*

Introduction

Histiocytic diseases are rare hematological neoplasms that can occur at any age. They are characterized by infiltrates of myeloid cells of the mononuclear phagocytosis system. The revised classification of histiocytoses [1] proposes a group of Langerhans-related diseases. These include Langerhans cell histiocytosis (LCH), indeterminate cell histiocytosis (ICH), Erdheim-Chester disease (ECD), and overlap of LCH and ECD. Infiltrates of LCH consist of dendritic cells and various inflammatory cells. LCH cells are positive for CD1a and CD207 (Langerin) on immunohistochemical staining. Granuloma formation and inflammation can cause tissue damage with dysfunction in any organ. Somatic mutations of the mitogen-activated protein kinase (MAPK) central signal transduction pathway have been identified in almost all cases [2]. These mutations all lead to the activation of kinases regulated by different extracellular signals (ERK). Considering experimental results on dendritic cells, it

can be assumed that the earlier these mutations occur in myeloid differentiation, the more extensive the disease pattern is [3].

Epidemiology

The annual incidence of LCH in a large national cohort was 3 to 8 cases per 1 million children and adolescents younger than 15 years, with a median age at diagnosis of 3.2 years [4]. In adults, the incidence is estimated to be 1 to 2 cases per 1 million adults [5]. However, it is unclear how many cases go unrecognized. The median age of adult patients was 35 years in the Histiocyte Society International Registry Study [6]. According to studies, females and males are affected about equally in both age groups. A clear risk factor for the development of LCH has not yet been identified. In adults, isolated lung involvement mainly occurs in smokers [7].

Clinical presentation

The disease can affect each organ individually (single system disease, SS) uni- (SS-s) or multifocally (SS-m) or multiple organs simultaneously (multisystem disease, MS). The proportion of primary SS-LCH is two-thirds in children and adults [4,8,9] and primary MS-LCH correspondingly one-third. However, in adults, studies reporting an inverse ratio of primary disease extent can be found [6,10]. This may be due to a clustering of more severely ill patients with this rare disease at specific centers. In children, the most commonly involved organs are the skeleton (80percentage), skin (33percentage), and pituitary (25percentage) [11]. The liver, spleen, hematopoietic system, and lungs are also frequently affected (15percentage each). Less frequently, involvement of lymph nodes (5-10percentage) and central nervous system (except pituitary) (2-4percentage) have been seen. In adults, the disease manifests particularly in the skeleton, lungs, skin, and pituitary region [12]. Involvement of mucous membranes and lymph nodes is not uncommon. Therapeutic studies of children have found that the manifestation of LCH in the hematopoietic system, spleen, or liver is associated with a worse prognosis [13,14,15]. Therefore, these organs have been defined as so-called organs at risk. In MS-LCH, studies stratify into a group with or without the involvement of organs at risk. So far, this finding could not be replicated in adults with LCH. In adults, these organs are rarely affected. Only one large Chinese study with in two-thirds primary MS-LCH and a larger proportion of patients with liver and spleen involvement could negatively impact event-free survival and, in the case of age above 50 years at diagnosis, also overall survival [10] .The extent to which involvement of bone marrow or even the central nervous system without pituitary worsens prognosis in adult patients is unclear. Furthermore, in children, lesions in craniofacial bones with particularly intracranial extension seem to represent risk lesions concerning the possible development of diabetes insipidus or neurodegeneration [16,17,18]. Specific locations with a recommendation for systemic therapy also include involvement of vertebral bodies with an intraspinal soft tissue component, involvement of the eyes and ears, intracerebral lesions (excluding the pituitary gland), and imaging or clinical signs of neurodegeneration. Based on the data, this concept does not translate unreservedly to the adult approach. For example, an evaluation of adult patients with the manifestation of LCH in craniofacial bones either as a single lesion or in association with other skeletal lesions did not reveal an increased risk concerning diabetes insipidus or neurodegeneration during the disease, even without systemic therapy [9]. Of note, however, was a high proportion of patients who already had primary osteolysis of craniofacial bone and diabetes insipidus.

Diagnosis

Diagnosis preferably requires histopathological assessment of tissue samples. According to the recommendations of an international expert consensus [19], the mutation status of the MAPK-ERK pathway should already be determined primarily in adult patients. In special cases with difficult histology acquisition, children with, e.g., conspicuous spinal findings can also be monitored closely. In adults with, e.g., typical radiological lung changes, the diagnosis of LCH can also be made likely by cytology of bronchoalveolar lavage and cell-free DNA analysis from peripheral blood to determine BRAF mutation status. Standardized diagnostic testing is required at any age to determine the extent of the disease. Physical examination should include the entire skin surface and the mucosal regions that can be seen. The thorax is examined radiologically. A supplementary high-resolution computed tomography (CT) can be performed if conventional images are insufficient. Due to the obligatory osteolytic appearance of bony manifestations, conventional radiographs of the skeleton or even a CT in low-dose technique are required. In children and adolescents, magnetic resonance imaging (MRI) of the skeleton may be considered, although abnormal findings require further conventional radiologic evaluation. A possible alternative is the combination of positron emission tomography (PET)

and CT. In particular, this allows more bony lesions to be detected and already visible changes to be assessed regarding their metabolic disease activity [20]. However, the radiation exposure is relatively high at 10-15 mSv. The central nervous system is examined by MRI, including administering a contrast medium. Abdominal organs are preferably assessed by ultrasound. Further measures, such as endoscopy with biopsy and organ puncture, depend on clinical symptoms, organ involvement, and the need for histological confirmation. Laboratory tests include whole blood count, coagulation, and clinical chemistry. Additional endocrinologic testing is indicated for evidence of hormonal disorders. In the case of etiologically unclear cytopenias or cytoses, bone marrow biopsy may be considered.

Therapy

The beginning, as well as the way of therapy, depends on the extent and activity of the disease with effects on the organ functions. The disease can be self-limiting, chronically relapsing, or rapidly progressive. Recurrent disease activity or reactivation is to be expected. Close monitoring or local therapy should be considered in patients with localized skin or unifocal bone involvement. Suitable options are the local application of, e.g., mustard to the skin or a bone biopsy with, if necessary, intralesional application of, e.g., depot methylprednisolone. Especially in children, major bone defects should be avoided by surgery or growth retardation by local radiotherapy. In adults, on the other hand, primary neurosurgical resections with spongiosaplasty or irradiation with 16 to 24 Gy are appropriate. The local recurrence rate in studies is 8.3percentage [9] after extirpations of osteolysis of the cranial dome or 9percentage after local irradiation [21]. Children with large or unfavorably localized bony single lesions and unifocal bone lesions at specific sites with increased risk of central nervous system involvement in the course are treated primarily with cytostatic therapy. This is also true for children with multifocal bone involvement. Currently, the impact of the duration of maintenance therapy (6 versus 12 months) is being evaluated in children with risk lesions for central nervous system involvement or multifocal bone lesions. These situations are usually treated locally in adults or by the supportive use of bisphosphonates [22]. Their efficacy and safety are not yet proven in children, although small studies have shown evidence of efficacy even in children with LCH [23]. In the case of isolated pulmonary involvement, strict smoking cessation is recommended, especially in adolescents and adults, because of the association with smoking. If further deterioration of lung function still occurs, immunosuppressive therapy with, e.g., overlapping prednisolone/azathioprine should be considered. About extensive cutaneous manifestations, immunomodulatory therapy with, e.g., thalidomide may also be a treatment option in adults. Systemic therapy is indicated in patients of any age with MS-LCH. International therapy studies in children showed that the standard therapy is based on the combination of prednisone and vinblastine [13]. Clinical response after the first six weeks represents a prognostic parameter [15]. Extending the duration of therapy from 6 to 12 months reduces the risk of relapse in MS-LCH [14]. Without a response to therapy or early disease relapse, other cytostatic agents may be considered, such as clofarabine, cladribine, and cytarabine. Comparable results to cytostatic chemotherapy have also been noted in smaller studies in adults with LCH. A standard therapy could not be identified. Rather, attention must be paid to the spectrum of side effects and the distribution of cytostatic drugs in different organs. Of note in adults is the high efficacy of aggressive polychemotherapy with long-lasting remissions [24] and the efficacy of the oral cytostatic drug hydroxyurea [25]. In children with high-risk LCH, allogeneic hematopoietic stem cell transplantation is an established therapeutic principle [26]. However, its value is still unclear compared with the combination therapy of cladribine and cytarabine. In contrast, life-threatening aggressive courses of LCH rarely occur in adults, which can be treated by autologous [27] or allogeneic stem cell transplantation [28]. Based on the detection of driver mutations of the MAPK signal transduction pathway in histiocytic diseases, targeted therapy of LCH is also possible. BRAF and MEK inhibitors have achieved impressive remissions in children and adults with LCH. However, relapses frequently occur after medication discontinuation, so the therapy duration is still open, at least in children. Their use is still reserved, particularly for repeatedly relapsing or refractory courses. However, it is noteworthy that even in clinical remission of LCH under MAPK inhibition, mutant mononuclear cells can persist in blood and bone marrow and are again detectable in increased numbers in the event of relapse after cessation of therapy [29]. This argues for a future combined use of conventional cytotoxic chemotherapy and MAPK inhibition with, however, increased toxicity. A therapeutic problem at any age is the involvement of the central nervous system. Here, nodular infiltrates in the pituitary gland, hypophysial stalk, and cerebrum and cerebellum are

most prominent. Therapy is performed with drugs or, in adults, with radiotherapy. If necessary, the hormonal substitution of the pituitary function must be observed. Less frequently, symmetrical infiltrations of the cerebellar peduncles, bridge, or basal ganglia are seen on imaging. Clinically, some patients present with accompanying coordination problems and neurocognitive and psychological abnormalities. The genesis of these neurodegenerative changes is unclear. Discussed is a paraneoplastic-induced activation of dendritic cells [30] or an active demyelinating process starting from mutant hematopoietic progenitor cells, from which the cells in other LCH lesions are also derived [31]. Therapeutically, immunosuppressive or cytostatic therapies were only sporadically effective. Positive results were observed after initial applications of CD20 antibody therapy [32] or therapy using a BRAF inhibitor [33].

Prognosis

Following the analyses of the French registry of children and adolescents under 18 years of age diagnosed with LCH from 1983 to 2012, the reactivation rate after 5 years was 47% in the cohort from 1983 to 1998 (483 patients) and 37% in the cohort from 1998 to 2012 (995 patients) [4]. Overall survival rates at 5 years improved from 92.7% to 98.7% in the cohorts. This was primarily attributed to improved treatment outcomes in patients with MS-LCH and risk organ involvement. In the earlier cohort, 42 patients (8.7%), and in the later cohort, 13 patients (1.3%) died. The Histiocyte Society International Registry included 274 adult patients with LCH (6). Regarding survival, 236 patients were evaluable, of whom 15 patients (6.4%) died. The overall 5-year survival rate for all patients was reported to be 92.3%. The 5-year event-free survival was 100% for patients with SS-LCH, 87.8% for lung involvement, and 91.7% for MS-LCH. In the German single-center study of 194 adult patients, 26.4% had reactivation during a median follow-up of 49 months [9]. This was mainly detectable in the organ system originally involved. Residual mortality and recurrence rates remain significant problems. In addition, in 30 to 40 % of children and adults with LCH, there are late sequelae caused by the disease or by the therapeutic measures taken. These manifest themselves as irreversible disturbances of hormonal glands, functional limitations of the lungs, and neurological disorders. However, due to bony destruction, disorders of the auditory and vestibular organs and tooth loss may also occur. While endocrine functional deficits can still be compensated by hormone substitution, the other disorders lead to invalidation and considerable impairment of the quality of life. Therefore, early diagnosis and, if necessary, initiation of therapy are essential to prevent organ dysfunction. The follow-up of patients should initially be structured and, in the further course, symptom-oriented and should record the disease activity, and the occurrence of possible late sequelae. This also includes the possibility of malignancy. The coincidence of LCH and malignancies is increased regardless of patient age [34]. Acute leukemias were particularly common in children and adolescents up to and including 18 years of age, and solid tumors and lymphomas occurred in adults with LCH. In childhood, acute lymphoblastic leukemia was more often detected before LCH. Acute myeloid leukemia or solid tumors were usually found after LCH, possibly attributed to chemotherapy and radiotherapy already given [11]. In adults, associated acute leukemias were usually diagnosed during or after the manifestation of LCH. Malignant lymphomas or solid tumors occurred preferentially before or concurrent with LCH. One explanation for the increased correlation between histiocytic diseases and malignancies could be the oncogenic mutations that are equally known in both disease groups, which have already been demonstrated in several cases [35]. LCH may also develop into a malignancy secondarily, such as Langerhans cell sarcoma [36].

Conclusion

The clinical picture of LCH in children and adults is very similar. On the other hand, involvement of the hematopoietic system, liver, and spleen is more common in children than adults and is associated with a worse prognosis. Specific disease localizations in children have been found, and they undergo primary systemic therapy due to a higher risk of developing diabetes insipidus or neurodegeneration. This has not yet been transferred to the course of the disease in adults. Radiological examinations are employed in diagnosis only to a limited extent in children due to radiation exposure. Only in exceptional situations is therapeutic surgery or radiation administered to youngsters. The pharmacological therapy range is comparable in both age groups. Too far, however, there is a lack of data on the safety and efficacy of BRAF and MEK inhibitors in children and adolescents. Furthermore, supportive therapy with bisphosphonate in children has yet to be established. Most affected patients have a good prognosis. However, the disease`s residual mortality, recurrence rates, and late sequelae necessitate additional efforts in its treatment.

Conflict of Interest

The authors declare no conflict of interest.

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