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Intracranial Rosai-Dorfman Disease: pathophysiology, diagnosis and treatment

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Abstract:

Introduction and purpose:

Rosai-Dorfman Disease (RDD), known also as sinus histiocytosis with massive lymphadenopathy (SHML) is a benign histiocytic proliferative syndrome. The etiology and pathogenesis of RDD remains unclear. Central nervous system involvement is a rare event and concerns approximately 7.8% of RDD cases, whereas intracranial lesions constitute almost 90% of CNS-RDD cases. The aim of this literature review was to summarize current knowledge about the diagnosis and treatment of intracranial manifestation of RDD. We also described possible hypotheses regarding the pathophysiology of this disorder.

State of knowledge:

Even though Rosai-Dorfman disease was thought to be a reactive process, recent evidence demonstrate the presence of clonality, which means that in this histiocytosis the process that underlies the pathology is neoplastic. Intracranial lesions caused by RDD can be easily misdiagnosed with many diseases such as meningiomas, malignant gliomas or metastatic tumors. The final diagnosis of Rosai-Dorfman disease should be made based on histologic and immunohistochemical examinations. Current therapeutic options for this condition include

surgery, radiotherapy, chemotherapy, corticosteroids and immunotherapy. Surgical treatment often constitutes the first-line treatment for intracranial RDD and is the most beneficial treatment option. However, the implementation of adjuvant therapies is very important to avoid the recurrence of lesions, which appear in approximately 14% of subjects after about 10 years from surgery.

Conclusion:

This literature review presents current data about pathophysiology, diagnosis and treatment of intracranial involvement of Rosai-Dorfman disease. Further studies on this topic should focus on exploring etiologic mechanisms underlying on this pathology and comparing available treatment methods.

Keywords: Rosai-Dorfman disease; histiocytosis; central nervous system; intracranial Rosai-Dorfman disease

1. Introduction

Rosai-Dorfman Disease (RDD), known also as sinus histiocytosis with massive lymphadenopathy (SHML) is a benign histiocytic proliferative syndrome described by Rosai and Dorfman in 1969 [1] . This non-Langerhans histiocytosis is a rare disorder with a prevalence about 1:200,000 people [2] . Most commonly, RDD occurs during the first or second decade of life and is presented by bilateral painless cervical lymphadenopathy coexisting with fever, elevated erythrocyte sedimentation rate, polyclonal hypergammaglobulinemia, and neutrophilia [3–5] . The etiology and pathogenesis of RDD remains unclear[6] . In 43% of cases, RDD is connected with extranodal involvement and refers to skin, cavum sinuses, orbit, bones and upper respiratory tract [7] . Central nervous system involvement is a rare event and concerns approximately 7.8% of RDD cases [8] . Intracranial lesions constitute almost 90% of CNS-RDD cases, whereas the cases of RDD involving spinal canal are significantly scarcer, but also have been observed [9] . The intracranial RDD lesions often are dural-based and circumscribed, and may mimics meningioma [10] . Rarely can be manifested as intraventricular masses [11] .

In this literature review, we summarized current knowledge about the diagnosis and treatment of intracranial RDD. We also described possible hypotheses regarding the pathophysiology of this disorder. The etiology of RDD still remains unknown and may be significant for discovering further treatment options based on targeting specific molecules essential for the pathological process in this condition.

2. Etiology and pathogenesis of RDD

One of the most popular paradigms concerning histiocytoses origin is whether the process is neoplastic or reactive - in LCH (Langerhans cell histiocytosis) it is already known that the neoplastic process is involved in this disease pathogenesis due to certain genes' activation [12–14] . Even though the histological evaluation shows alterations in cellularity and accumulation of activated, large histiocytes with abundant eosinophilic cytoplasm and atypical nuclei accompanied by inflammatory background or fibrosis [15–18] , exact genes were tackled in RDD people, which demonstrates the neoplastic origin of this disease [19–23] . Recent research suggests that RDD onset is correlated with the excessed immune response of the haematolymphoid system to infection, which leads to transferring circulating monocytes into activated macrophages (not dendric cells) - future histiocytes [24] . The cellularity is high with plenty of lymphocytes, enlarged histiocytes and emperipolesis, sometimes accompanied by neutrophils and plasma cells as well [18]. Previously RDD histiocytes were thought to be polyclonal, reactive and non-malignant [25] . Cells express CD14, CD163, CD68 and fascin. They are CD1a- and CD207- and are strongly S100 positive[21,26,27] .

Up to 33% of patients express abnormalities in KRAS, NRAS, MAP2K1 and ARAF genes, which are correlated with the neoplastic origin [19–23,28]. Some cases go along with familial heredity, especially in families with a germline mutation in the SLC20A3 gene[29] . RDD appears more frequently in people with immunological dysregulates (autoimmune diseases, lymphomas)[26,30,31] . Another important predictive prognostic marker is OCT2 [32] .

3. Diagnosis of intracranial RDD

3.1. Radiological features

There is a lack of characteristic, pathognomonic symptoms in radiological imaging of Rosai–Dorfman disease. The most frequently found radiological image presents a single intracranial mass, multiple lesions also have been noted [33,34] . Intracranial masses are homogeneously enhanced, located on the base of the dura mater, external to the brain parenchyma with vasogenic edema [35,36] . Moreover, changes are well-restricted and located on convexities regions, parasagittal, cranial base, sellar and super-sellar areas [37,38] .

Intracranial mass on CT without contrast presents as an iso- or hyperdense [39] . Moreover, this image can be linked with the erosion of the neighboring bone[40,41] . On this diagnostic imaging surrounding oedema and homogeneous enhancement appears [33] .

Masses on MRI images are mainly isointense on T1-weighted imaging with heterogenous, distinct intensification. On T1-weighted imaging with gadolinium contrast dural tail sign is often present [42] . RDD lesions are iso- or low hyperintense on T2-weighted MRI [10,40,42–46] . The macrophages producing free radicals during phagocytosis might be the reason of presence T2-weighted areas with low intensity [47] .

What is more, fluorodeoxyglucose positron emission tomography/computed tomography can be used in diagnosing relapsed intracranial Rosai-Dorfman disease, this was outlined by Deshayes et al. who used this method to diagnose relapsed RDD of the hypothalamus [48] .

3.2. Pathological features

Histologic and immunohistochemical examinations are pathologic examinations that can prove a final diagnosis of Rosai-Dorfman disease [49] .

Common histological findings contain lymphocytes, plasma cells, foamy macrophages and huge, clear-cut histiocytes with phagocytic vacuoles [50–53] . Histiocytes in Rosai-Dorfman disease are pale and have oval or round vesicular nuclei with clear-cut nuclear membranes and single nucleoli and create patterns with lymphoplasma cells which infiltration is weakened [2] . Histologically, sometimes eosinophils and neutrophils may be present [2] . What is more, in extranodal involvement of RDD fibrosis can be present.

Emperipolesis is a distinguishing but not a specific feature of RDD, it is only current in 87% of RDD in CNS [54,55] . This histological hallmark consists in the presence and penetrating of an intact cell without cytoplasm another living cell. In Rosai-Dorfman disease mature lymphocytes, erythrocytes and plasma cells are located in histiocytes' phagocytic vacuoles [37,50,56] . Specific immunohistochemical stains are needed because of the lack of identifiable infectious agents related to mixed, dense and chronic inflammatory infiltrate with a significant histiocytic component [50,57] . The presence of histiocytes is confirmed by positive staining for CD68, CD163 and S-100 protein. Moreover, cells are immunoreactive for HAM 56, α1 chymotrypsin, Mac 387, α1 antitrypsin, Ki-1 and lysozyme, but negative for CD1a and EMA [33,58–64] .

3.3. Differential diagnosis

Rosai-Dorfman disease might be mistaken with other diseases like meningiomas, malignant gliomas, metastatic tumors, pseudotumors, lymphomas, histiocytosis X, tuberculosis, neurofibromatosis, sarcoidosis and granulomatous diseases [40,65] .

Radiographically, RDD can be mistaken with meningioma, both diseases are dura-based and extra-axial lesions [50] . Things, that can help with differentiation are facts that meningioma in angiographic studies shows an absence of hypervascularity and on T2-weighted images of Rosai-Dorfman disease low hyperintense areas are present. In contrast to RDD, meningiomas are usually hypervascular lesions. What is more, on CT images in the case of meningioma hemorrhages or calcifications might be seen [10] , common in meningiomas are also hyperostosis and bone erosion in contrast to RDD [42,50] . Magnetic resonance spectroscopy can also be helpful with the differentiation of RDD and meningioma, in the case of RDD choline peak reaches 140 ppm, but the second disease shows an alanine peak on 48 ppm [43] .

The presence of CD68 and S-100 indicates histiocytes. Therefore infectious diseases and granulomatous can be excluded [50] . Positive staining for S-100 can exclude Erdehim-Chester disease, but can not eliminate Langerhans cell histiocytosis [66] , which is also S-100 positive. Differentiation is possible thanks to CD1a, CD207 and V600E negativity in RDD [25,56,58,61] . Moreover, histiocytes in Langerhans cell histiocytosis show reniform or indented nuclei and Birbeck granules are present [67–71] .

4. Treatment of intracranial RDD

Although RDD is considered a benign condition and almost 50% of cases of sporadic RDD demonstrate spontaneous recovery without application of any treatment, remission is not observed in the case of intracranial RDD [6] . Current therapeutic options for this condition include surgery, radiotherapy, chemotherapy, corticosteroids and immunotherapy. However, no unified treatment scheme has been established and therapy should be tailored for the individual patient depending on their clinical presentation [16] .

4.1. Surgical resection

Surgical treatment often constitutes the first-line treatment for intracranial RDD. In many of cases, surgery is performed when RDD is misdiagnosed as meningioma based on clinical and radiological findings. Complete surgical resection is the most beneficial treatment option. It improves neurological symptoms and provides tissue for histopathological diagnosis. Gross-total resection (GTR) can be obtained in the majority of intracranial RDD cases and results in long-term satisfactory outcomes [6] . However, RDD lesions may be located in deep brain structures or surrounded by vital neurovascular structures. Thus, GTR is difficult, sometimes even impossible to obtain in these cases [72,73] . Biopsy or subtotal resection performed for such cases significantly increase the risk of RDD recurrence [6] . About 14% of subjects relapse after subtotal resection after about 10 years from surgery [3,64] . Therefore patients after surgical treatment should be clinically and radiologically observed. Regular MRI scans and PET FDG/CT scans can be both useful for this purpose [74] . Moreover, the implementation of adjuvant therapies should be considered[73] . Indeed, the combinatory approach for intracranial RDD demonstrated very satisfactory results [39] .

In surgical management of pediatric intracranial RDD staged surgery with 3-5 monthly operation time intervals should be considered due to its better toleration and therapeutic outcomes [75] . Long-term radiological follow-up is necessary and adjuvant treatment may be similarly implemented as in the case of adult intracranial RDD [75] .

4.2. Radiotherapy

Radiation therapies are a popular component of adjuvant treatment for intracranial RDD after subtotal resection. Some authors demonstrated the effectiveness of fractionated radiotherapy and stereotactic radiotherapy in relief of the RDD symptoms, especially in the case of recurrent intracranial RDD [16,76] . However, their efficacy remains unclear due to the lack of quality, randomized studies, and variety of patients' responses observed after these therapies[73,77–79] . A recent systematic review by Tripathi et al, evaluating the use of stereotactic radiosurgery in intracranial histiocytoses, including 2 cases of RDD, emphasized the role of stereotactic radiotherapy in the alternative treatment of intracranial RDD [80] . However, their cohort contained an insufficient number of patients to formulate clear conclusions. Furthermore, there are proposed options, which may increase the efficacy of radiation therapies in RDD including radioenhancers and brachytherapy [81,82] .

4.3. Steroid therapy

Administration of corticosteroids for RDD with intracranial involvement was suggested by some studies [53,77] . Steroid therapy has also demonstrated favorable effects on the reduction of multiple and isolated intracranial masses[83–85] . Moreover, its non-invasiveness constitutes a great advantage among available treatment methods. Thus, steroids can be considered for alternative treatment of RDD not suitable for surgical resection. However, in certain cases recurrence of symptoms and no response to treatment with corticosteroids was demonstrated by some patients [74,86] .

4.4. Chemotherapy

Different chemotherapeutic schemes were used for the treatment of RDD, although the best therapeutic approach for intracranial involvement of RDD has not been established yet [87] . Chemotherapeutic agents investigated in the literature for RDD treatment include methotrexate, anthracyclines, cytarabine, vinca alkaloids, 6-mercaptopurine, etoposide and 2-chlorodeoxyadenosine [6,88–90]. However, their various efficacy raises the question of the use of chemotherapy for RDD treatment.

4.5. Immunotherapy

Recent research gives more and more data about the pathogenesis of RDD. This provides an opportunity to use the immunotherapeutic approach for the treatment of this disease. Some authors reported beneficial effects of the use imatinib (a tyrosine kinase inhibitor) and rituximab (CD20 monoclonal antibody) in therapy of systemic RDD [91,92] . However, their efficacy has not been evaluated in the case of RDD with intracranial involvement. Further studies should investigate the potentially effective targeted agents for treatment of intracranial RDD.

5. Conclusion

The Rosai-Dorfman Disease is a rare syndrome, which in certain cases may involve the central nervous system. Even though Rosai-Dorfman disease was thought to be a reactive process, recent evidence demonstrate the presence of clonality, which means that in this histiocytosis the process that underlies the pathology is neoplastic.

Intracranial lesions caused by RDD can be easily misdiagnosed with many diseases such as meningiomas, malignant gliomas or metastatic tumors. Despite the rarity and benign character of this condition, CNS-involving RDD requires adequate therapy and it should be considered in the differential diagnosis when intracranial mass is discovered. Furthermore, in certain cases, intracranial RDD can manifest with malignant behavior and poor prognosis [57] .

The rarity of intracranial RDD hinders performing high-quality, randomized controlled studies. Thus, the clinical efficacy of available treatment methods is difficult to investigate and

compare. Furthermore, it impedes creating appropriate recommendations for the treatment of this condition. However, based on existing reports, surgical treatment combined with strict, long-term follow-up and adjuvant treatment constitute the best therapeutic approach.

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