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Two illustrative cases of adult Lhermitte-Duclos disease and a systematic review of literature related to surgical management

Goran Lakicevic [a], Selma Tinjak-Demic [b], Sandra Lakicevic [c], Senta Frol [d,e], Bruno Splavski [f,g,*]

[a] Department of Neurosurgery, Mostar University Clinical Hospital, Mostar, Bosnia and Herzegovina
[b] Department of Neurology, Mostar Cantonal Hospital, Mostar, Bosnia and Herzegovina
[c] Department of Neurology, Mostar University Clinical Hospital, Mostar, Bosnia and Herzegovina
[d] Department of Vascular Neurology, University Medical Center, Ljubljana, Slovenia
[e] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[f] Department of Neurosurgery, Dubrovnik General Hospital, Dubrovnik, Croatia
[g] Faculty of Applied Health Sciences, University of Zagreb, Zagreb, Croatia

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ABSTRACT

Background: Lhermitte-Duclos disease is a rare subtype of gangliocytoma, a benign tumor growth in the cerebellum often associated with Cowden syndrome, a sporadic genetic pleomorphic disorder that is inherited in an autosomal dominant manner and caused by a harmful mutation in the *PTEN* gene. Such a mutation can originate malignant and benign tumors, including dysplastic gangliocytoma of the posterior cranial fossa.
Methods: We present two illustrative cases of Lhermitte-Duclos disease that we encountered and surgically treated during the last few years. We also performed a systematic literature review concerned with the surgical management of Lhermitte-Duclos disease and Cowden syndrome.
Results: Both patients were young females complaining of occipital headaches and underwent brain MRIs that revealed unilateral discrete cerebellar atrophy and expansive lesions of the posterior cranial fossa with characteristic striate T-2 weighted hyperintensity resembling tiger fur. They were both successfully operated on due to the posterior fossa dysplastic gangliocytoma, which was histopathologically confirmed as Lhermitte-Duclos disease. In one patient, genetic testing confirmed a *PTEN* mutation characteristic for Cowden syndrome.
Conclusion: Early diagnosis, genetic testing, and close monitoring are obligatory to enhance the knowledge of Lhermitte-Duclos disease and its probable association with Cowden syndrome to decrease the risk of malignancy of other organs and organic systems. Surgical posterior fossa decompression is required at the onset of neurological symptoms to relieve the mass effect and provide tissue samples for further analysis, ensuring a favorable outcome.

1. Background

Lhermitte-Duclos disease (LDD) is a rare, benign lesion within the cerebellum, classified as a tumor subtype of gangliocytoma—specifically, dysplastic cerebellar gangliocytoma. It consists of dysplastic ganglion cells and is typically located in the posterior fossa, with a generally favorable prognosis. It is frequently associated with Cowden syndrome, a sporadic autosomal dominant pleomorphic disorder caused by pathogenic mutations in the phosphatase and tensin homolog (PTEN) gene (Dhamija and Hoxworth, 2020). Cowden syndrome is a familial condition characterized by dysplasia across the endodermal, mesodermal, and ectodermal layers, resulting in both malignant and benign tumors (Takaya et al., 1999), including dysplastic gangliocytomas in the posterior cranial fossa. Recognizing this association is of clinical importance, as careful monitoring of LDD patients may reveal undiagnosed Cowden syndrome and facilitate the early detection of malignancies (Robinson and Cohen, 2006; Prabhu et al., 2004).

In this paper, we present two illustrative cases of LDD treated by partial surgical tumor resection at our institution over the past few years. Additionally, we systematically reviewed the PubMed database literature on LDD and Cowden syndrome's surgical management in adults, discussing the outcome and potential genetic links between these

* Corresponding author. Faculty of Applied Health Sciences, University of Zagreb Mlinarska 38, 10 000, Zagreb, Croatia.
E-mail addresses: goran.laki@gmail.com (G. Lakicevic), selma.tinjak@gmail.com (S. Tinjak-Demic), sandra.juric@gmail.com (S. Lakicevic), senta.frol@gmail.com (S. Frol), splavuno@gmail.com (B. Splavski).

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two rare disorders.

2. Material and methods

2.1. Study objectives

The primary objective was to present two illustrative cases of adult LDD patients and discuss its surgical management, the and outcome, as well as its possible genetic association with Cowden syndrome.

The second objective was to systematically review the literature related to the surgical management of LDD patients.

2.2. Searching methods

On April 2025, we searched the PubMed database in English using terms such as adult LDD, Cowden syndrome, surgical resection, conservative treatment, and relapse.

The extent of surgical resection was defined in three different categories such as total tumor resection, partial tumor resection, and unknown range of tumor resection.

The literature search was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

All PubMed abstracts related to the objective but not written in English, as well as those unrelated to the search terms, were excluded from the analysis.

The searched articles were collected, selected, and independently reviewed by two researchers.

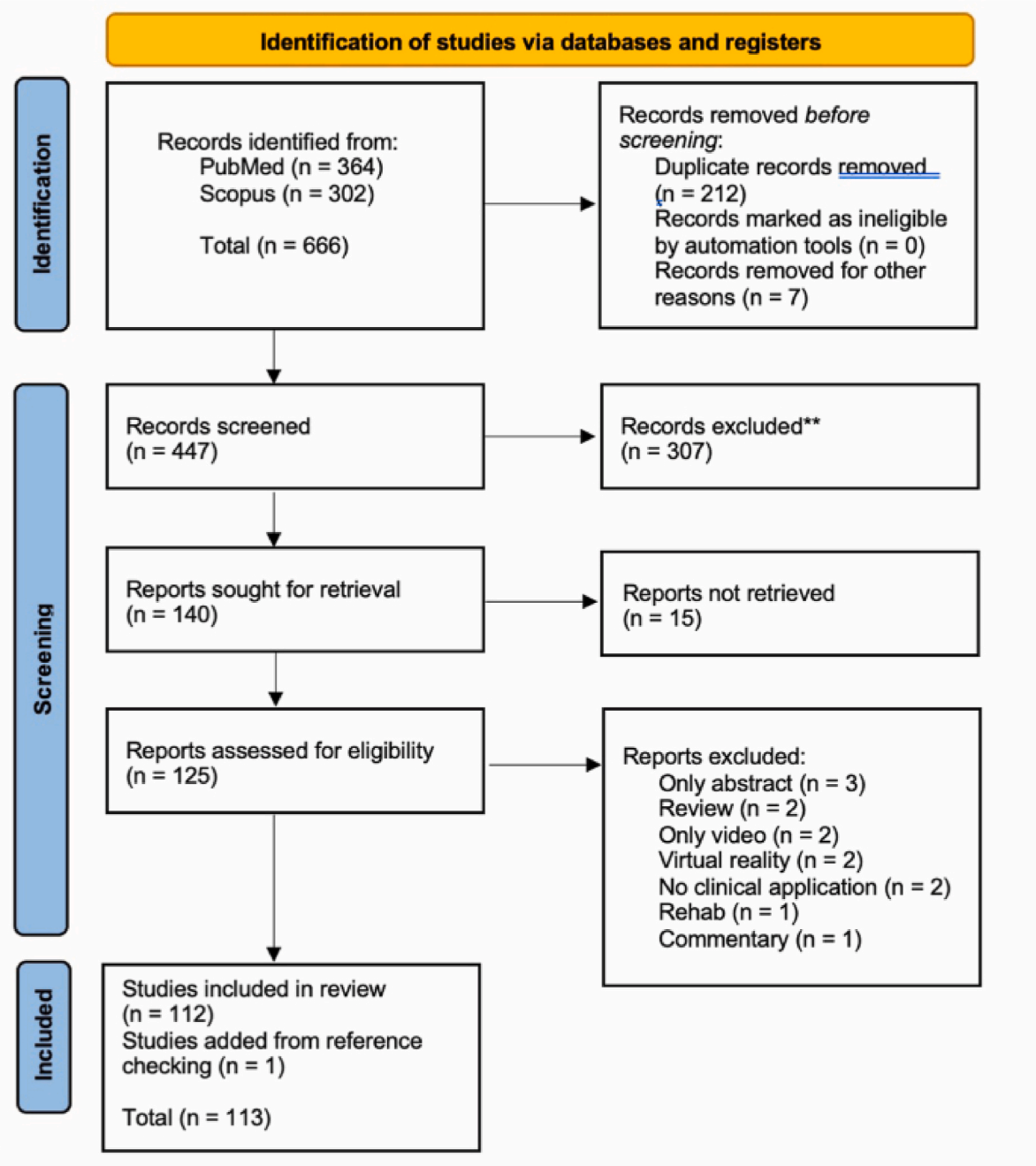

Fig. 1. Flowchart of the literature search.

3. Results

We extirpated and screened 236 articles from 246 identified papers, out of which 31 articles were sought for retrieval. Twenty-one of these articles were assessed for eligibility and included in the systematic review as new studies (Fig. 1). These 21 articles mentioned the method of surgical management ranging from partial tumor resection identified in 8 papers (Hashimoto et al., 1997; Ishizaki et al., 1997; Khandpur et al., 2019; Li et al., 2021; Liu et al., 2021; Matsumoto et al., 2015; Wang et al., 2024; Yuasa et al., 1997) to total tumor resection identified in 6 papers (Al-Noman et al., 2023; Ashraf et al., 2022; Bozbuga et al., 2010; Milbouw et al., 1988; Nowak and Trost, 2002; Su et al., 2024). In the remaining 7 papers, the method of surgical resection remained unknown (Gama and Almeida, 2017; Ozeren et al., 2014; Peltier et al., 2006; Prabhu et al., 2004; Shimanskiy et al., 2015; Zou et al., 2012; Williams et al., 1992).

4. Case presentation

The first case involves a 35-year-old female diagnosed with LDD and Cowden syndrome based on her medical history of multiple neoplasms. Over several years, she developed several skin hamartomas, dermatological lesions on her mucous membranes, and sclera. Additionally, she had a relapsing benign mesenchymoma in the region of the first metacarpal bone on her left hand, which was surgically treated in childhood. She also had recurrent fibroadenomas of the right breast, which were successfully resected ten and one year ago, respectively. Furthermore, she suffered from polycystic ovarian syndrome, a hormonal disorder characterized by androgen imbalance.

Upon admission, the patient presented with frequent occipital headaches, but her neurological examination was normal. A T-2 weighted MRI brain scan in axial and coronal reformations showed a characteristic striate, laminar tiger-pattern lesion in the left cerebellar hemisphere, consistent with dysplastic cerebellar gangliocytoma (Fig. 2a and b). The patient underwent surgery for posterior fossa dysplastic gangliocytoma, with only partial tumor resection achieved, and recovered well (Fig. 2 c). The surgery aimed to relieve the posterior fossa from the mass effect and provide tumor tissue samples for further analysis. After obtaining informed consent, genomic DNA was extracted from whole blood, revealing a *PTEN* mutation.

Follow-up investigations did not reveal any signs of disease progression or tumor recurrence during a ten-year clinical and radiological monitoring period (Fig. 2 d).

The second case involved a 33-year-old female with no previous neurological history, admitted due to sudden loss of consciousness accompanied by gastric aura and vomiting. A brain MRI revealed a heterogeneous space-occupying lesion with the characteristic tiger-striped pattern in the right cerebellar hemisphere and vermis, with compression of the fourth ventricle leading to slight lateral ventricular enlargement (Fig. 3a–d). She underwent a right suboccipital osteoplastic craniotomy with a supracerebellar subtentorial approach. Intraoperative ultrasound revealed hyperechogenic zones interspersed with healthy cerebellar folia. Tumor tissue was partially resected and histopathologically analyzed, confirming the presence of dysplastic ganglion

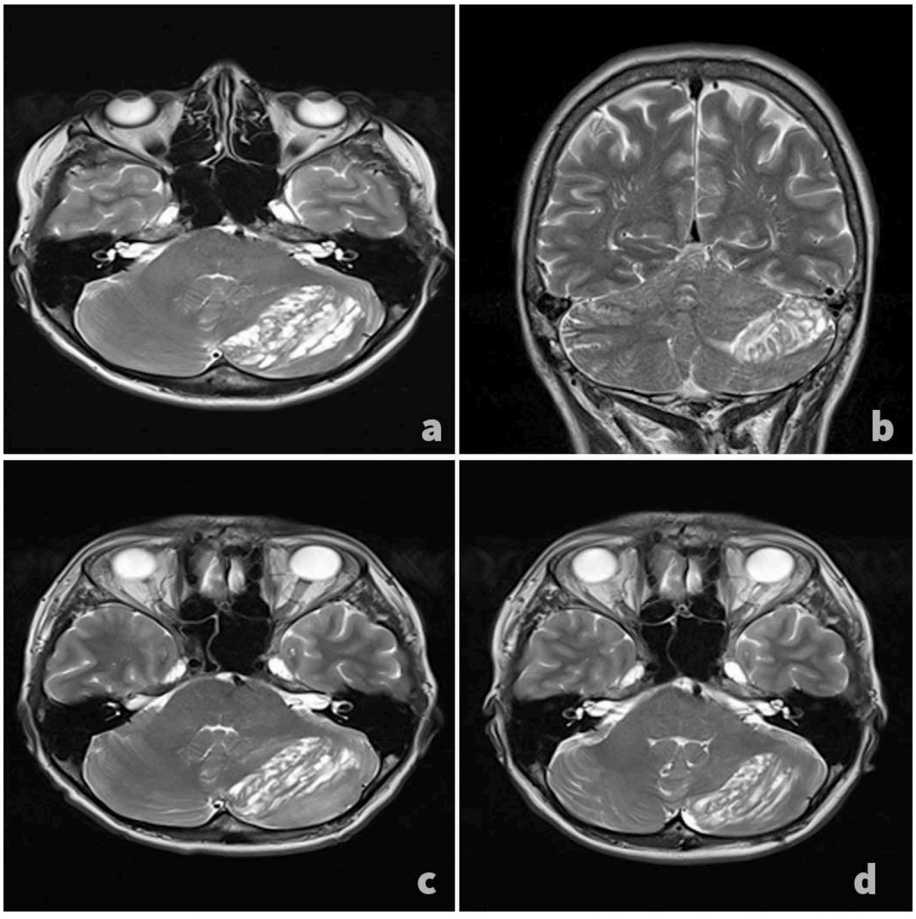

Fig. 2. The cerebellar cortex was unilaterally altered left, with a characteristic striate, laminar tiger pattern easily noticeable on preoperative native T-2 weighted (**a**) MRI scan, as well as on coronal reformation (**b**), which was indicative of dysplastic cerebellar gangliocytoma. Immediate postoperative T-2 weighted axial MRI brain scan revealing partial tumor resection, resulting in the relief of the mass effect on the posterior fossa (**c**). A postoperative T-2 weighted axial MRI brain scan of the same patient performed 10 years after surgery revealing no signs of tumor relapse and disease progression.

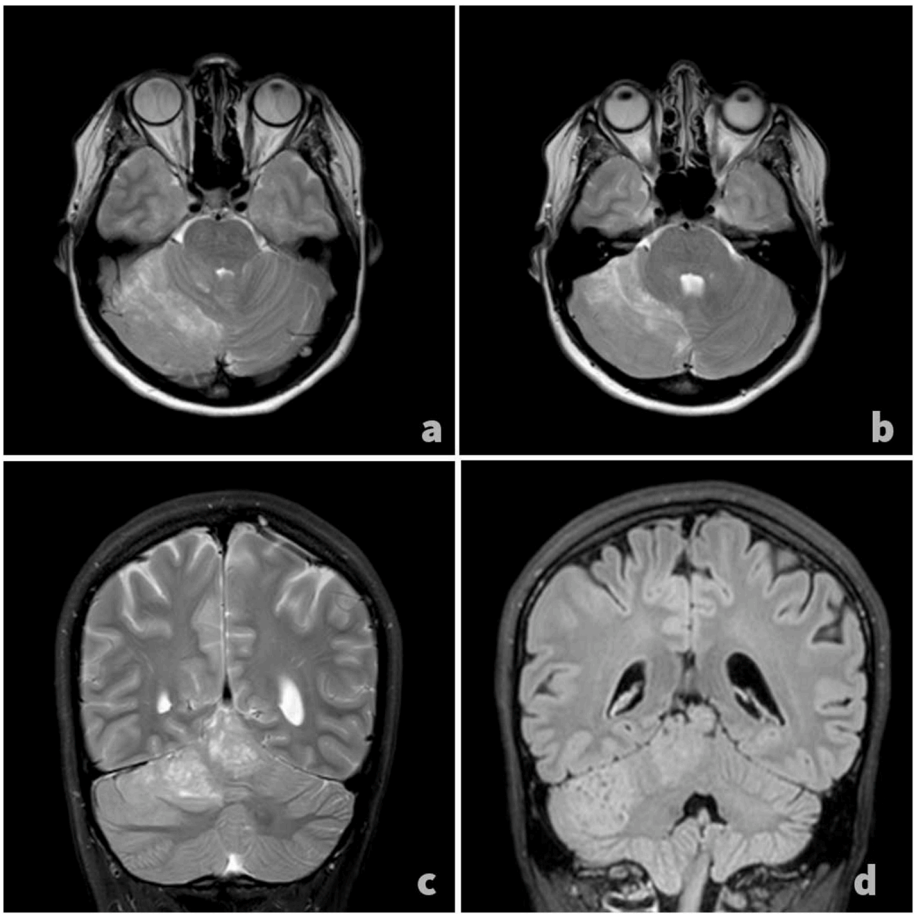

Fig. 3. A preoperative T-2 weighted and FLAIR-wighted MRI scan in axial (**a**) and coronal (**c**) reformation revealed a characteristic striate, laminar tiger pattern lesion of cerebellar parenchyma in the right hemisphere and vermis area indicative of dysplastic cerebellar gangliocytoma (**a-d**). Compression of the fourth ventricle was also observed, leading to a slight lateral ventricular enlargement (c).

cells in the molecular and inner granular layers of the cerebellum. These cells disrupted normal cerebellar architecture and were diagnosed as dysplastic gangliocytoma. Immunohistochemical analysis showed that the ganglion cells were synaptophysin and MAP2-positive but negative for CD34, IDH1, and GFAP, with no evidence of proliferative activity (Ki-67).

Postoperatively, the patient had an uneventful recovery and was discharged without neurological deficits. Further diagnostic tests for systemic malignancies were negative during a two-year follow-up. Genetic testing revealed the absence of a *PTEN* mutation. However, at a one-year follow-up, postoperative MRI scanning revealed a remaining tumor in the right cerebellar hemisphere and mediocranial vermis (Fig. 4).

5. Discussion

Although considered a malformative rather than a neoplastic disorder, LDD remains a rare and sporadic disease, with only 200–300 cases reported to date (Alanazi et al., 2023; Ma et al., 2019). We have identified two additional cases within the last few years.

A thorough understanding of the radiological and histological features of LDD, combined with a high index of suspicion, is essential for accurate diagnosis. Timely diagnosis should prompt investigations to evaluate potential associations with Cowden syndrome (Kolhe et al., 2023). Brain MRI T-2 weighted scans are pivotal in the diagnosis, with the characteristic unilateral striate, tiger-stripe hyperintensity of the cerebellar hemisphere being a hallmark of the disease (Joo and Doumanian, 2020; Nair et al., 2011; Zhang et al., 2022). Both patients in our series exhibited this radiological feature on preoperative T-2 weighted MRIs.

When neurological symptoms arise due to the mass effect of cerebellar gangliocytoma, complete surgical resection is typically required (Revuelta-Gutiérrez et al., 2023). However, achieving complete resection can be challenging due to difficulties in delineating the tumor from healthy tissue, making incomplete resection the common way of surgical management (Buhl et al., 2003; Jiang et al., 2017). Accordingly, we performed a systematic literature analysis related to the surgical management and identified that partial tumor resection was achieved in a simple majority of adult LDD patients yielding satisfactory outcomes (Hashimoto et al., 1997; Ishizaki et al., 1997; Khandpur et al., 2019; Li et al., 2021; Liu et al., 2021; Matsumoto et al., 2015; Wang et al., 2024; Yuasa et al., 1997). Both of our patients underwent surgery, but complete removal was not achieved, and they have since been monitored clinically and radiologically. No tumor recurrence was recorded during the extended follow-up.

Lhermitte-Duclos disease is notably associated with Cowden syndrome, and the two conditions share the same genetic basis. Lhermitte-Duclos disease is the most common type of brain lesion in adults with Cowden syndrome (Joo and Doumanian, 2020). The incidence of Cowden syndrome is estimated to range from 1 in 200,000 to 250,000 in the general population (Farooq et al., 2010; Nelen et al., 1999), with a higher prevalence in women, likely due to the frequent occurrence of breast and uterine tumors. Once a diagnosis of either LDD or Cowden syndrome is made, a thorough examination for the other disorder is essential, as it may identify malignant lesions associated with Cowden syndrome (Derrey et al., 2004). In our series, both patients were young

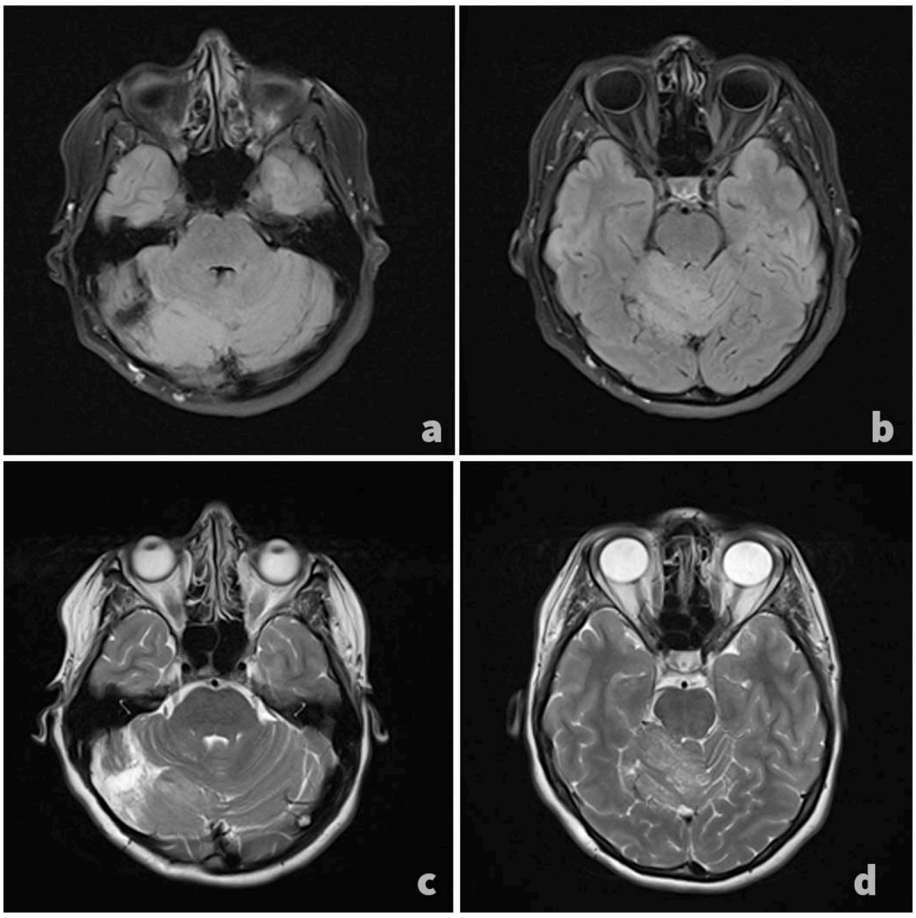

Fig. 4. Immediate postoperative T-2 and FLAIR-weighted MRI scans in axial reformation revealed a residue of the tumor process in the right cerebellar hemisphere and the mediocranial vermis (**a, b**). No further tumor recurrence was revealed on axial T-2 weighted MRI scans at a two-year checkup (**c, d**).

women, with one presenting with a breast fibroadenoma and polycystic ovarian syndrome. Her genetic testing confirmed a *PTEN* mutation.

Approximately 30–35 % of patients with LDD meeting the clinical criteria for Cowden syndrome exhibit a detectable *PTEN* mutation (Pilarski, 2019). A systematic review by Alanazi et al. found that 32.8 % of LDD patients were associated with Cowden syndrome, and 19.9 % had a confirmed *PTEN* mutation (Alanazi et al., 2023). Located on chromosome 10q23.31, *PTEN* is a tumor suppressor gene, whose mutations lead to dysregulated tumor growth and angiogenesis, increasing the risk of various tumors, including CNS abnormalities (Miguelote et al., 2020). However, the presence of *PTEN* mutations does not always correlate with clinical manifestations of Cowden syndrome (Arai et al., 2023).

The early recognition of LDD, including genetic testing and consistent monitoring, is crucial, as it is often associated with Cowden syndrome and an increased risk of cancer in multiple organs (Monjarás-Romo et al., 2023). As such, early diagnosis significantly improves patient outcomes (Pîrlog et al., 2024). Both of our patients underwent genetic testing, and one had a confirmed genetic and clinical association with Cowden syndrome.

Close long-term follow-up is mandatory for LDD patients to detect potential recurrence (Uchida et al., 2018), or spread to other organs and organic systems in the case of Cowden syndrome. Both of our patients were carefully monitored over extended periods without evidence of tumor relapse and/or disease progression.

This report highlights the management and outcomes of two cases of adult Lhermitte-Duclos disease, a rare disorder in the literature. We also discuss the clinical, radiological, and histopathological characteristics of LDD and its association with Cowden syndrome. The systematic review of the literature related to surgical management revealed that a simple majority of reported adult cases were treated by partial tumor resection.

The paper's contribution to the existing literature consists of accumulating two more illustrative cases to the already restricted and scarce body of LDD and Cowden syndrome cases. Remembering the recent all-encompassing meta-analysis (Alanezi et al., 2023), our systematic review was primarily aimed at the aspect of methods of surgical tumor resection in adult LDD patients and its relationship to the outcome. However, the retrospective nature and small sample size of this case series and systematically reviewed articles limit the generalizability of our findings. Further research involving larger cohorts is needed to confirm these results.

6. Conclusion

Adult Lhermitte-Duclos disease is a rare form of gangliocytoma, typically located in the posterior fossa. Early diagnosis, genetic testing, and regular follow-up are essential for better understanding the disease and its potential link to Cowden syndrome. Recognizing this association is crucial, as it can facilitate the early detection of malignancies in other organs. Surgical posterior fossa decompression is necessary when neurological symptoms occur, contributing to favorable outcomes and prognosis. Partial tumor resection seems to be a preferred way of surgical management in adult LDD patients revealing no further tumor relapse and disease progression.

Submission declaration and verification

Submission of the article implies that the work described has not been published previously (except in the form of an abstract, a published

lecture, or academic thesis), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or any other language, including electronically without the written consent of the copyright holder.

Ethics approval

The present manuscript complies with the guidelines for human studies, and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This manuscript did not require ethical approval in accordance with local/national guidelines.

Consent to participate

Written consent has been obtained from the patients involved.

Consent for publication

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix. Structured Review

Structured Review

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