ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.surgicalneurologyint.com

Surgical Neurology International

Editor-in-Chief: Nancy E. Epstein, MD, Professor of Clinical Neurosurgery, School of Medicine, State U. of NY at Stony Brook.

SNI: Neuro-Oncology

Editor
Mitsutoshi Nakada, MD
Kanazawa University, Ishikawa, Japan

SNI
Open Access

Review Article

Lhermitte–Duclos disease: A systematic review

Aued Iaed Alanazi[1], Tariq Alanezi[1], Ziyad Fahad Aljofan[1], Alwaleed Alarabi[1], Sherif Elwatidy[2]

[1]Department of Surgery, College of Medicine, King Saud University, [2]Department of Neurosurgery, King Saud University, Riyadh, Saudi Arabia.

E-mail: *Aued Iaed Alanazi - auedalanazi@gmail.com; Tariq Alanezi - alanezitariq@gmail.com; Ziyad Fahad Aljofan - ziyadaljofan@gmail.com; Alwaleed Alarabi - aralwaleed@gmail.com; Sherif Elwatidy - smfwat@yahoo.com

***Corresponding author:**
Aued Iaed Alanazi,
College of Medicine,
King Saud University, Riyadh,
Saudi Arabia.

auedalanazi@gmail.comp

Received: 01 July 2023
Accepted: 02 September 2023
Published: 29 September 2023

DOI
10.25259/SNI_555_2023

Quick Response Code:

ABSTRACT

Background: Lhermitte–Duclos disease (LDD) is a rare tumor, with only about 300 reported cases. It often shows comorbidity with Cowden syndrome (CS); however, it can occur by itself. Radiologically, the "tiger-stripe" appearance is considered pathognomonic. Surgical resection remains the mainstay of treatment. This report aims to describe the clinical and radiological characteristics of LDD and its relationship with CS according to age group.

Methods: PubMed electronic databases were searched in August 2022. The search terms included "Lhermitte–Duclos disease" and "dysplastic gangliocytoma," which yielded 297 and 103 research articles, respectively. The articles were collected and reviewed by three researchers.

Results: Out of 400 identified articles, we analyzed 302 reported cases. The mean age at presentation was 33.6 ± 16 years; 171 patients (56.6%) were female, and 123 (40.7%) were male. The most commonly reported symptom was headache (174 patients, 57.6%), followed by ataxia (109, 36.1%). In addition, 99 cases (32.8%) were associated with CS, and 60 (19.9%) had a confirmed phosphatase and tensin homolog (*PTEN*) mutation. A tiger-stripe appearance was observed in 208 cases (58.7%); surgical resection was performed in 64.2% of the cases. Mortality and recurrence rates were 4.3% and 8.6%, respectively. No statistically significant difference was found between adult- and pediatric-onset LDD for the association with CS ($P = 0.128$).

Conclusion: Our findings suggest that adult and pediatric LDD have major commonalities; however, further prospective studies are warranted.

Keywords: Cowden syndrome, Disease onset, Lhermitte–Duclos disease, Phosphatase and tensin homolog

INTRODUCTION

Lhermitte–Duclos disease (LDD) or dysplastic gangliocytoma of the cerebellum is a benign, rare, hamartomatous lesion characterized by a slow and progressive abnormal growth in the cerebellum.[28] In general, the clinical features of this benign entity are directly related to the anatomical location of the lesion in the posterior fossa. Lesions in the posterior fossa usually cause clinical symptoms related to the mass effect on the cerebellum and ventricular system, including headaches, hydrocephalus, visual disturbances, and cerebellar signs and symptoms. Although LDD is not considered malignant, its clinical presentation is not always benign or straightforward.[30]

Given the association between LDD and Cowden syndrome (CS), numerous non-neurological signs and symptoms suggest the existence of such a lesion. LDD was introduced in 1920 by

Lhermitte and Duclos,[25] who described the case of a 36-year-old man with a 10-month history of occipital headache and left-sided hearing impairment. The patient suddenly developed vertigo, recurrent falls, and gait ataxia. Subsequently, the patient became confused and disoriented, eventually succumbing to coma and death.[25]

Surgical intervention for LDD was described in 1937 by Christensen, who reported a patient with LDD who underwent surgery and was discharged from the hospital without complaints.[5] Since then, an increasing number of cases have been reported, demonstrating the lesion's rarity and complexity. However, the nature of the lesion has no established consensus. Lhermitte and Duclos suggested that it might be a congenital malformation and a neoplasm of ganglion cells; contrastingly, other studies have suggested that it might be a blastoma, hamartoma, or hyperplasia of normal tissue.[29]

The epidemiology of LDD remains unclear, with over 300 cases being reported worldwide. Most cases occur between the 2nd and 4th decades, with no apparent sex predominance.[29] The epidemiology of LDD is usually described from the perspective of its association with CS. Although the frequency of comorbid LDD and CS remains unclear, frequencies of 1.8%, 6%, and 15% have been reported.[31] The lesion usually develops in the infratentorial region, having an insidious onset with a good overall prognosis.[12,22]

The histopathological characteristics of LDD include the absence of the Purkinje cell layer; increased thickness of the molecular cell layer, which yields axon over-myelinization; hypertrophy of the granular cell layer; replacement of the granular cell layer with dysplastic cortical neurons; and atrophy of cerebellar white matter.[12] Notably, LDD is radiographically characterized by increased myelinization and vacuolization of axons associated with the tumor. Accordingly, magnetic resonance imaging (MRI) can visualize a characteristic layered pattern.[1] The lesion is usually hypointense on T1-weighted imaging (T1WI) and produces alternating high- and low-intensity levels on T2-weighted imaging (T2WI), producing the characteristic "tiger-stripe" pattern.[49] Although this pattern is highly specific, it has been observed in other lesions.

The management of LDD is usually simple, with surgical resection reserved for symptomatic patients; cerebrospinal fluid (CSF) diversion is performed in patients who develop signs and symptoms of increased intracranial pressure. Systemic chemotherapeutic agents are not prescribed. Although other modalities have been used, including molecularly targeted therapies, evidence remains insufficient.[20]

CS is a rare, autosomal dominant, multisystem clinical entity characterized by malignant and hamartomatous lesions developing across the body, particularly in the breast, endometrium, and thyroid. CS is caused by a germline mutation in the phosphatase and tensin homolog (*PTEN*) gene, a tumor suppressor gene found on human chromosome 10q23.[31] This phosphatase regulates signal transduction in the phosphatidylinositol 3-kinase/PTEN/AKT pathway, which regulates essential cellular processes, including growth, cell migration, and apoptosis.[14] The estimated prevalence of CS ranges between 1 in 200,000 and 1 in 250,000. CS appears to have a female predominance, which can be attributed to including breast and uterine lesions. Further, most cases occur among Caucasians. The age at diagnosis of CS is 13–65 years. However, these data were reported before the consortium criteria for CS diagnosis were developed.[13] The main diagnostic criteria, as reported by Pilarski,[33] include breast cancer, endometrial cancer, thyroid cancer, gastrointestinal hamartoma, macrocephaly, macular pigmentation of the glans of the penis, multiple mucocutaneous lesions, and adult LDD. Minor criteria include autism spectrum disorder, mental retardation, colon cancer, lipoma, renal cell carcinoma, and several other lesions.[33] The management of CS usually involves tumor screening and prevention.

Although >300 cases of LDD have been reported, research remains insufficient. Specifically, the proportion of cases that recur after surgical resection, the mortality rate of the lesion, and the number of cases associated with CS and *PTEN* mutations, especially in the pediatric population, remain unclear. This systematic review aimed to describe the clinical characteristics of LDD and its radiological appearance with different conventional MRI sequences. In addition, we aimed to assess the association of adult and pediatric LDD with CS and *PTEN* mutations, reported surgical and medical management protocols, and the recurrence and mortality rates of LDD.

MATERIALS AND METHODS

Study objectives

The primary study objective was to review the clinical characteristics, radiological appearance, genetic associations, and outcomes in reported cases of LDD. In addition, we aimed to evaluate differences between adult- and pediatric-onset LDD regarding their association with CS.

Search methods

We queried the PubMed database using the search terms "Lhermitte–Duclos disease" and "dysplastic gangliocytoma," yielding 297 and 103 articles, respectively. The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Inclusion and exclusion criteria

We did not include the first report of LDD by Lhermitte and Duclos[25] since it was absent from PubMed. We included all published studies from 1956 to August 2022 that reported at least one case of LDD and at least one of the following data: age, sex, clinical presentation, radiological presentation, CS status, *PTEN* mutations, management options, and clinical outcomes. CS was diagnosed based on the opinion of the authors of each case report. For cases published before the international consortium of CS criteria for diagnosis or before the discovery of the association between LDD and CS (n = 11 cases), the diagnosis of CS was confirmed by the authors of the current article using the international consortium of CS criteria for diagnosis and features reported by the original authors.

Selection of studies

The eligibility of identified articles was independently evaluated by three authors (AA, TA, and ZA) through an initial screening of the title and abstract, followed by a full-text review. We included all studies that reported relevant information regarding the predetermined set of variables. The study excluded articles lacking the given variables, non-human cases, non-English articles, LDD-mimicking cases, and reviews that did not report a new case. In addition, we excluded all cases in which data could not be retrieved. Disagreements were resolved by agreement of at least two of the three reviewers [Figure 1].

Data collection

We extracted the following data from the original articles: demographic data, clinical presentation, CS status, presence of *PTEN* mutations, radiological presentation, management protocol, recurrence, and mortality.

RESULTS

We extracted 302 reported cases from the 400 identified articles. Demographic, clinical, and radiological data

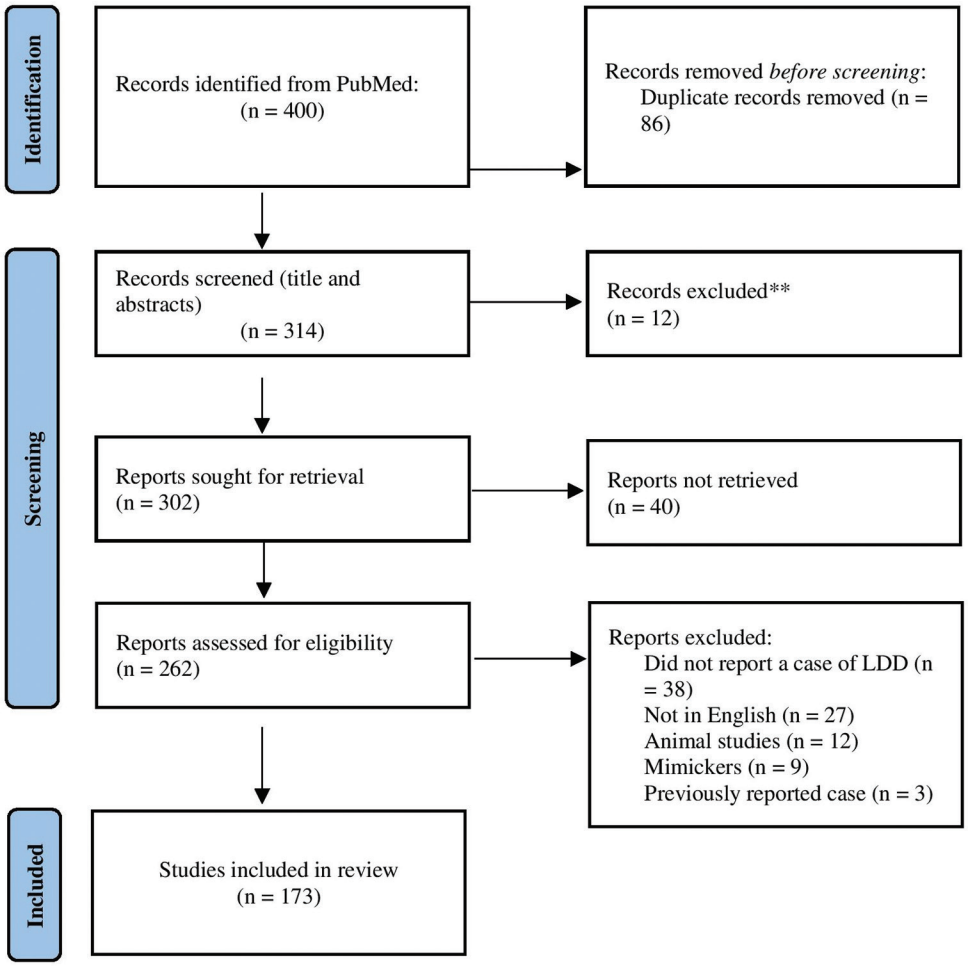

Figure 1: Flowchart of the search process. n: Sample size, LDD: Lhermitte-Duclos disease

were collected from original articles. Descriptive analyses were performed using IBM SPSS Statistics for Windows version 25. Fisher's exact test was performed to assess differences between adult- and child-onset LDD related to CS, recurrence, and mortality rates.

Demographics

At presentation, the mean age (± standard deviation) was 33.6 ± 16 years, ranging between 3 days and 77 years. We divided patients into two groups based on their age; specifically, patients aged <18 years and >18 years were included in the pediatric (47 patients, 15.6%) and adult (247 patients, 81.8%) groups, respectively, with only eight patients (2.6%) having data missing for age. For sex distribution, female patients (171, 56.6%) outnumbered male patients (123, 40.7%) [Table 1].

CS and *PTEN* mutation

LDD was associated with CS in 99 patients (32.8%) and not associated in 42 (13.9%); 161 patients (53.3%) lacked data. Moreover, LDD was associated with *PTEN* mutations in 60 cases (19.9%) and not associated and 42 (13.9%); 161 cases (53.3%) lacked relevant information [Table 1].

Clinical presentation

Regarding the clinical presentation of LDD, the most common symptom was headache ("occipital" or "global;" *n* = 174, 57.6%), followed by ataxia (*n* = 109, 36.1%); cerebellar signs, including dysmetria and dysdiadochokinesia (*n* = 68, 22.5%); papilledema (*n* = 61, 20.2%); visual disturbances (*n* = 51, 16.9%); dizziness (*n* = 40, 13.2%); nausea (*n* = 36, 11.9%); vomiting (*n* = 35, 11.6%); diplopia and strabismus, usually involving eye abduction secondary to abducens cranial nerve palsy and elevated intracranial pressure (*n* = 29, 9.6%); nystagmus (*n* = 24, 7.9%); vertigo (*n* = 22, 7.3%); and altered mental status (*n* = 16, 5.3%). Several cases did not mention the patient's clinical presentation; 13 cases (4.3%) reported them incidentally [Table 2].

Table 1: Demographic characteristics, Cowden syndrome, and *PTEN* mutation status (*n*=302)

Age of presentation (*n*=302)	Mean (SD) in years	33.6 (16)
	Minimum age	3 days
	Maximum age	77 years
	Pediatric	47 (15.6%)
	Adults	247 (81.1%)
	NA	8 (2.6%)
Sex	Male	123 (40.7%)
	Female	171 (56.6%)
	NA	8 (2.6%)
PTEN mutation	Yes	60 (19.9%)
	No	16 (5.3%)
	NA	226 (74.8%)
Cowden syndrome	Yes	99 (32.8%)
	No	42 (13.9%)
	NA	161 (53.3%)

NA: Not Available, LDD: Lhermitte–Duclos disease, PTEN: Phosphatase and tensin homolog, *n*: Sample size, SD: Standard deviation

Radiological presentation

Among the 302 cases, only 208 reported radiological findings; the reported lesions were usually unilateral. The right cerebellar hemisphere (*n* = 81, 39%) was more affected than the left (*n* = 75, 36.1%). Only 12 patients (5.7%) presented with bilateral lesions; 4 (1.9%) had midline lesions involving only the vermis. The lesion site was not described in 36 cases (17.3%). Enhancement patterns (usually mild) were present in 31 patients (14.9%) and absent in 82 (39.4%); 95 (45.7%) cases lacked relevant information.

Regarding the characteristic findings of LDD, a classic tiger-stripe appearance was described in only 122 cases (58.7%). The mass effect on adjacent structures was present in 75 cases (36%) and absent in 1 case (0.5%); the other cases lacked relevant data (63.5%). Tonsillar herniation was reported in 43 cases (20.7%); similar results were found for hydrocephalus, with 59 patients (28.4%) presenting radiological signs of increased intracranial pressure. Six reports denied any apparent hydrocephalus; 143 reports had no relevant data.

Signal intensity of LDD in conventional MRI

Regarding intensity, the lesion had a low signal on T1WI in 99 cases (47.6%), a mixture of low and isointensity in 5 cases (7.2%), and a solely isointense pattern in 2 cases (1%). No relevant data were available regarding T1WI in 92 cases (44.2%). On T2WI, isointensity was reported in only 1 patient (0.5%). In most cases (*n* = 118, 56.7%), the lesion

Table 2: Clinical presentation of 302 cases (*n*=302)

Headache	174 (57.6%)
Ataxia	109 (36.1%)
Cerebellar signs	68 (22.5%)
Papilledema	61 (20.2%)
Visual disturbance	51 (16.9%)
Dizziness	40 (13.2%)
Nausea	36 (11.9%)
Vomiting	35 (11.6%)
Diplopia+strabismus	29 (9.6%)
Nystagmus	24 (7.9%)
Vertigo	22 (7.3%)
Altered mental status	16 (5.3%)
Incidental	13 (4.3%)

n: Sample size

appeared hyperintense. Mixed intensities were reported in two different presentations: mixed isointensity and hyperintensity (n = 11, 5.3%) and mixed hypo- and hyperintensity (n = 1, 0.5%) [Table 3].

Management of LDD

Conservative management was performed in 14 patients (4.6%), with many refusing treatment. Conservative management included using analgesics, antiemetics, and radiological monitoring (MRI). The type of management was not described for 94 patients (31.1%). Surgical intervention was performed in 194 patients (64.2%). Non-surgical interventions were also reported: 2 patients (0.7%) received chemotherapy and 1 (0.3%) received radiotherapy. CSF diversion was established in 48 patients (15.9%), with the most common method being ventriculoperitoneal shunting (n = 35, 11.6%), followed by external ventricular draining (n = 9, 3%) and ventriculoatrial shunting (n = 1, 0.3%). The CSF diversion method was not specified in 3 cases (1%).

The extent of resection was defined in three different categories. Specifically, gross-total resection (GTR), subtotal resection (STR), and partial resection were indicated by resection of ~100%, 50–100%, and <50% of the lesion, respectively. GTR, STR, and partial resection were reported in 46 (15.2%), 59 (19.5%), and 23 (7.6%) patients, respectively [Table 4].

Postoperative course

Favorable and unfavorable outcomes were reported in 157 (52%) and 4 (1.3%) cases, respectively; the remaining cases had no data regarding the postoperative course. The complication rate was 9.6% (29 patients). Recurrence was observed in 26 patients (8.6%), among whom 11 were associated with CS. Recurrence was not observed in 80 patients (26.5%); 196 cases (64.9%) lacked information regarding recurrence. Death was reported in only 13 patients (4.3%); the remaining cases denied death (n = 91, 30.1%) or had no data regarding death (n = 198, 65.6%) [Table 4].

The most common complications were persistent cerebellar symptoms (n = 8, 2.65%), followed by seizures (n = 5, 1.66%) and cerebellar mutism and respiratory difficulty (n = 3, 1%). Hydrocephalus, shunt infection, and ventriculitis were observed in 2 patients (0.7%) each. Other rare complications included encephalomalacia, diabetes insipidus, global cerebral ischemia, vision deterioration, and hypotension [Table 5]. Among the reported deaths, the causes were aspiration pneumonia (n = 2), metastatic breast cancer (n = 2), myocardial infarction (n = 2), intestinal obstruction (n = 1), intratumoral hemorrhage (n = 1), respiratory failure (n = 1), and sigmoid stenosis (n = 1); three patients did not have a caused determined [Table 6].

Table 3: Radiological characteristics of LDD (n=208)

Site of the lesion	RCH	81 (39)
	LCH	75 (36.1)
	Bilateral	12 (5.7)
	Vermis only	4 (1.9)
	NA	36 (17.3)
Enhancement	Yes	31 (14.9)
	No	82 (39.4)
	NA	95 (45.7)
Tiger-stripe appearance	Yes	122 (58.7)
	No	0 (0%)
	NA	86 (41.3)
Mass effect on adjacent structures	Yes	75 (36)
	No	1 (0.5)
	NA	132 (63.5)
Tonsillar herniation	Yes	43 (20.7)
	No	1 (0.5)
	NA	164 (78.8)
Hydrocephalus	Yes	59 (28.4)
	No	6 (2.9)
	NA	143 (68.8)
Intensity		
T1WI	Hypointense	99 (47.6%)
	Mixed (low and iso)	5 (7.2%)
	Isointense	2 (1.0%)
	NA	92 (44.2%)
T2WI	Isointense	1 (0.5%)
	Mixed (iso and high)	11 (5.3%)
	Mixed (low and high)	1 (0.5%)
	Hyperintense	118 (56.7%)
	NA	77 (37%)

NA: Not Available, LDD: Lhermitte–Duclos disease, RCH: right cerebellar hemisphere, LCH: Left cerebellar hemisphere, T1WI: T1 weighted image, T2WI: T2 weighted image, n: Sample size

LDD and age-related association with CS

No significant differences were found between adult- and pediatric-onset LDD for association with CS, mortality rate, and lesion recurrence, with P = 0.128, 0.728, and 0.426, respectively [Table 7].

DISCUSSION

Since the first case of LDD was reported in 1920 by Lhermitte and Duclos,[24] many cases have been subsequently reported, especially with advances in neurological imaging techniques. As of August 2022, more than 300 cases have been reported. A milestone in the history of LDD was the discovery of an association between LDD and CS, called Cowden–Lhermitte–Duclos (COLD) disease. To the best of our knowledge, this systematic review is the first for LDD in English literature.

Table 4: Management and postoperative course (*n*=302)

Type of treatment	Conservative	14 (4.6%)
	Surgical	194 (64.2%)
	NA	94 (31.1%)
Non-surgical interventions	Chemotherapy	2 (0.7%)
	Radiotherapy	1 (0.3%)
CSF diversion	EVD/ventriculostomy	9 (2.98%)
	VP shunt	35 (11.6%)
	VA shunt	1 (0.3%)
	Did not specify	3 (1%)
Resection	GTR	46 (15.2%)
	STR	59 (19.5%)
	Partial	23 (7.6%)
Postoperative course	Favorable	157 (52%)
	Unfavorable	4 (1.3%)
	NA	141 (46.7%)
Complications	Yes	29 (9.6%)
	No	273 (90.4%)
Recurrence	Yes	26 (8.6%)
	No	80 (26.5%)
	NA	196 (64.9%)
Mortality	Yes	13 (4.3%)
	No	91 (30.1%)
	NA	198 (65.6%)

NA: Not Available, EVD: External ventricular drain, VP: Ventriculo-peritoneal, VA: Ventriculo-atrial shunt, GTR: Gross total resection, STR: Subtotal resection, n: Sample size

Table 5: Complications (*n*=302)

Cerebellar mutism	3 (1%)
Encephalomalacia	1 (0.3%)
Persistent cerebellar symptoms	8 (2.65%)
Diabetes insipidus	1 (0.3%)
Global cerebral ischemia	1 (0.3%)
Worsening vision	1 (0.3%)
Hypotension	1 (0.3%)
Hearing loss	1 (0.3%)
Hydrocephalus	2 (0.7%)
Seizures	5 (1.66%)
Headache	1 (0.3%)
Respiratory difficulty	3 (1%)
Meningitis	1 (0.3%)
Otitis media	1 (0.3%)
Ptosis	1 (0.3%)
Blindness	1 (0.3%)
Shunt infection	2 (0.7%)

n: Sample size

Age, sex, and demographics

The mean age of presentation was consistent with LDD occurring mainly in the 2nd and 4th decades of life.[29] LDD being primarily an adult disease might explain the predominance of COLD syndrome in adult-onset LDD. In addition, LDD occurs more frequently in females.

Table 6: Cause of death (*n*=302)

Aspiration pneumonia	2 (0.7%)
Intestinal obstruction	1 (0.3%)
Intratumoral hemorrhage	1 (0.3%)
Metastatic breast cancer	2 (0.7%)
Myocardial infarction	2 (0.7%)
Respiratory failure	1 (0.3%)
Sigmoid stenosis	1 (0.3%)
Not mentioned	3 (1%)

n: Sample size

Table 7: Relationship between the adult and pediatric populations in terms of the association with CS, mortality, and recurrence

	Adult LDD	Pediatric LDD	*P*-value
Cowden syndrome			
Yes	86	13	0.128
No	30	10	
Mortality			
Yes	11	2	0.728
No	67	22	
Recurrence			
Yes	22	4	0.426
No	61	19	

LDD: Lhermitte–Duclos disease, CS: Cowden syndrome
All cases that did not report "Yes" or "No" were removed to enhance the representation of the data.

CS and genetic association

LDD was associated with CS and *PTEN* mutations in one-third and one-fifth of cases, respectively. However, many of these cases were diagnosed before the international consortium of CS criteria for diagnosis was developed.[11] Based on the revision of the criteria by Pilarski *et al*.,[31] fewer patients would be eligible for a CS diagnosis given the lack of required information in some reported cases. We believe that the data are too heterogeneous to evaluate the diagnostic accuracy solely based on the reported information about patient status.

Pérez-Núñez *et al*.[30] suggested that LDD be considered a typical lesion of CS. They, further, indicated that LDD was often comorbid with "other" pathologies rather than as an isolated case, suggesting that LDD is a component of CS. However, only one-third of the cases in our review were associated with CS. Moreover, we believe that this percentage is exaggerated because many of these cases did not meet the diagnostic criteria proposed by Pilarski *et al*.[31] In contrast, almost two-thirds of our patients had isolated LDD.

CS and the onset of LDD

The association of CS with LDD is further complicated by the distinction between adult- and childhood-onset LDD. Zhou

et al.[50] found that none of the pediatric patients with LDD (n = 3) exhibited CS features or *PTEN* mutations, suggesting that adult-onset LDD should be considered a pathognomonic criterion for CS. Our review identified 13 pediatric patients with LDD associated with CS; four reported *PTEN* gene mutations, one denied any mutations, and eight did not report data regarding *PTEN* mutations. These data suggest that the distinction between adult- and childhood-onset LDD might have a weak scientific basis [Table 8].

In addition, no significant difference between adult and pediatric patients was found for the prevalence of CS, recurrence, or mortality. However, given the heterogeneity of the reported data, the retrospective nature of this review, and the short follow-up duration, we could not determine the exact differences between these age groups. Moreover, definitions for the pediatric population have been inconsistent. In our review, we applied the relatively common definition of an age <18 years for the pediatric population. Zhou *et al*. described 18 patients, among whom 15 had confirmed germline mutations in the *PTEN* gene, and all were adults. This result demonstrates the importance of differentiating between adult- and pediatric-onset LDD. On immunohistochemistry, 75% of cases showed a loss of *PTEN* protein expression.[50] Most of the mutations were germline, but some patients also had somatic mutations.[50]

Bilateral involvement and the genetic origins of LDD

This review identified 46 patients with CS and *PTEN* mutations, representing 46.5% of those with both LDD and CS. This result is consistent with the previous reports and supports the overall premise of focusing less on the role of *PTEN* in the pathogenesis of isolated LDD.[32] This idea is, further, demonstrated in cases with bilateral LDD involvement; 12 patients (5.7%) showed bilateral involvement, but none had proven *PTEN* mutations, and only two were diagnosed with CS. This finding is inconsistent with previous suggestions that the pathogenesis of LDD involves *PTEN* mutation primarily[50] and raises skepticism regarding the widely reported genetic origins of the disease.[23] Furthermore, a low recurrence rate was observed in patients with bilateral lesions; although only two patients showed recurrence, both were diagnosed with CS [Table 9].

Radiological appearance

The appearance of LDD is usually described as a non-enhancing, well-circumscribed lesion, unilateral in the cerebellum, with low signal on T1WI, high signal on T2WI, and fluid-attenuated inversion recovery, and presenting the tiger-stripe appearance.[32,47]

Tiger-stripe appearance and enhancement

This review is the first large-scale report on the prevalence of enhancement, tiger-stripe appearance, and mass effect of LDD on MRI. The finding that lesion enhancements and linear striations were observed in 14.9% and 58.7% of cases is consistent with a previous small-scale review of 21 patients that found that 61.9% of the patients manifested the classical layered pattern.[16] However, the tiger-stripe appearance is not unique to LDD, and it should be combined with other typical signs of LDD to enhance diagnosis.[16] Although MRI seems to have a reasonable level of specificity for LDD, recognizing that other lesions may mimic the MRI findings of LDD is important.[8,21]

Enhancement is not rare in LDD. Different enhancement patterns were observed in 14.9% of cases; however, most had mild enhancement. In the aforementioned review, only 5 patients (23.8%) showed heterogeneous enhancement,[16] further supporting the argument for the diverse nature of LDD.

Magnetic resonance spectroscopy (MRS) and LDD malignancy

MRS can assess the chemical content of a given lesion, enabling differentiation of malignancy degrees through the measurement of chemical metabolites such as choline, N-acetylaspartate (NAA), and lactate.[15] In general, increasingly malignant tumors usually have increased choline/NAA and lactate levels.[49]

Zhang *et al*.[49] recently described the use of MRS for LDD. They confirmed that all patients with LDD showed a peak in lactate levels, which usually indicates a more anaerobic neuronal metabolism commonly associated with malignant transformation. However, they observed a decrease in the choline/NAA ratio in most patients, a characteristic finding of tumors with low malignancy. They concluded that using MRS and susceptibility-weighted imaging (SWI), along with conventional MRI, could be beneficial in differentiating LDD from other malignant mimickers.[49]

Management, postoperative course, and recurrence

Most patients in our review (64.2%) underwent surgical management, with 19.5% undergoing STR. The extent of resection seems to have a strong correlation with LDD recurrence.[1] An immunohistochemical analysis of 31 cases of LDD suggested that LDD recurrence might be attributed to two primary elements: the spatial heterogeneity of LDD, which yields non-concentrated and multifocal involvement of the cerebellar hemisphere, and partial lesion resection, as some of the genetically affected cells can look completely normal.[1] Very few studies have conducted long-term follow-up assessments. In a series of 12 patients, nine had a subtotal

Table 8: Pediatric LDD cases associated with Cowden syndrome

Case no.	Authors	Year	Age	Sex	*PTEN*	CS
1	Marano SR *et al.*[26]	1988	13	Female	NA	Yes *
2	Eng C *et al.*[10]	1994	14	Female	NA	Yes
3	Vinchon *et al.*[45]	1994	16	Female	NA	Yes
4	da Silva AA *et al.*[6]	1996	7	Male	NA	Yes
5	Iida S *et al.*[18]	1998	15	Male	Yes	Yes
6	Sutphen R *et al.*[41]	1999	9	Female	Yes	Yes
7	Robinson S *et al.*[36]	2000	9	Female	NA	Yes
8	Vantomme *et al.*[43]	2001	15	Female	NA	Yes
9	Pérez-Núñez *et al.*[30]	2004	12	Male	NA	Yes
10	Robinson *et al.*[37]	2006	17	Female	NA	Yes
11	Shimanskiy *et al.*[40]	2015	17	Female	Yes	Yes
12	Wang *et al.*[46]	2017	16	Female	No	Yes
13	Akmubarak *et al.*[2]	2019	17	Female	Yes	Yes

*Confirmed by the authors of this paper according to the international consortium of CS criteria for diagnosis
NA: Not available, LDD: Lhermitte–Duclos disease, PTEN: Phosphatase and tensin homolog, CS: Cowden syndrome

Table 9: LDD characteristics of patients with bilateral involvement of the cerebellum

Case no.	Authors	Year	Sex	Age (in years)	*PTEN*	CS	Recurrence	Outcome
1	Dietlein *et al.*[7]	1992	NA	3 days	NA	NA	NA	NA
2	Shanley *et al.*[39]	1992	Male	35	NA	NA	NA	Favorable
3	Verheggen *et al.*[44]	1994	Male	22	NA	NA	NA	Favorable
4	Tuli *et al.*[42]	1997	Female	54	NA	NA	NA	Favorable
5	Pérez-Núñez *et al.*[30]	2004	Male	12	NA	Yes	Yes	NA
6	Puri *et al.*[34]	2006	Male	24	NA	No	NA	NA
7	Bozbuga *et al.*[4]	2010	Female	28	NA	No	No	Favorable
8	Zak *et al* [48]	2017	Female	21 days	NA	NA	NA	Favorable
9	Dutta *et al.*[9]	2018	Male	7	NA	NA	No	Favorable
10	Borni *et al.*[3]	2019	Male	50	NA	NA	NA	NA
11	Khandpur *et al.*[23]	2019	Male	50	No	Yes	Yes	Favorable
12	Jiang *et al.*[19]	2020	Male	16	No	No	NA	Favorable

NA: Not available, PTEN: Phosphatase and tensin homolog, CS: Cowden syndrome

or partial resection with an average follow-up of 89 months, and only one case reported recurrence.[46] Similar results were found in another series of eight patients who underwent partial resection or STR.[20]

Of the 26 patients that experienced recurrence, 11 had a CS mutation and one had a *PTEN* mutation; 15 underwent subtotal or partial resection, four underwent GTR, and seven lacked information regarding the extent of resection. After treatment, four patients died, and seven experienced posttreatment complications.

Nonsurgical interventions and conservative management

Chemotherapy and radiotherapy were reported in two and one case, respectively. One patient had received ten cycles of metronomic temozolomide over 12 months; the patient developed nausea and vomiting. The second patient received rapamycin, a first-generation mechanistic target of rapamycin (mTOR) kinase inhibitor. The mTOR protein controls cell growth, survival, and proliferation.[38] However, surgical management and GTR remain the main treatment.[17,27-35] Conservative management was performed in 4.6% of cases. Since LDD shows slow growth and usually does not invade adjacent structures, a wait-and-see approach can be feasible as an alternative for GTR.

Limitations of this study

First, given the rarity of LDD, most of the literature consists of subjective reports of isolated cases. Second, we could not establish causal relationships due to the heterogeneity of the reported data, the review's retrospective nature, and the rarity of the disease. Further, research should investigate the differences between pediatric- and adult-onset LDD regarding CS association and follow-up. Moreover, the lack of consensus on the diagnosis of CS and differences in the definition of pediatric populations further restrict our understanding of LDD.

CONCLUSION

LDD is a rare tumor with many uncertainties and mimickers but generally has a good prognosis. One-third of the cases are associated with CS, and a highly specific radiological appearance can sometimes be observed. This systematic review found no apparent differences between adult- and pediatric-onset LDD for their association with CS. However, further prospective evaluations of this association should be conducted to enhance understanding of this disease.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author(s) confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Abel TW, Baker SJ, Fraser MM, Tihan T, Nelson JS, Yachnis AT, *et al.* Lhermitte-Duclos disease: A report of 31 cases with immunohistochemical analysis of the PTEN/AKT/mTOR pathway. J Neuropathol Exp Neurol 2005;64:341-9.
2. Almubarak AO, Haq AU, Alzahrani I, Shail EA. Lhermitte-Duclos disease with cervical arteriovenous fistula. J Neurol Surg A Cent Eur Neurosurg 2019;80:134-7.
3. Borni M, Kammoun B, Kolsi F, Abdelmouleh S, Boudawara MZ. The Lhermitte-Duclos disease: A rare bilateral cerebellar location of a rare pathology. Pan Afr Med J 2019;33:118.
4. Bozbuga M, Gulec I, Suslu HT, Bayindir C. Bilateral Lhermitte-Duclos disease. Neurol India 2010;58:309-11.
5. Christensen E. About ganglion cell tumors in the brain. Virchows Arch Pathol Anat Physiol Klin Med 1937;300:567-81.
6. da Silva AA, Banerjee T, Coimbra RL. Lhermitte-Duclos disease (cerebellar gangliocytoma). South Med J 1996;89:1208-12.
7. Dietlein M, Schröder R, Widemann B, Benz-Bohm G. Dysplastic gangliocytoma of cerebellum in a newborn. Diagnosis by ultrasonography and MRI. Pediatr Radiol 1992;22:131-3.
8. Douglas-Akinwande AC, Payner TD, Hattab EM. Medulloblastoma mimicking Lhermitte-Duclos disease on MRI and CT. Clin Neurol Neurosurg 2009;111:536-9.
9. Dutta G, Singh D, Saran RK, Singh H, Srivastava AK, Jagetia A. Childhood Lhermitte-Duclos disease progressing to medulloblastoma in bilateral cerebellar hemispheres: Report of unusual case. World Neurosurg 2018;117:344-9.
10. Eng C, Murday V, Seal S, Mohammed S, Hodgson SV, Chaudary MA, *et al.* Cowden syndrome and Lhermitte-Duclos disease in a family: A single genetic syndrome with pleiotropy? J Med Genet 1994;31:458-61.
11. Eng C. Will the real Cowden syndrome please stand up: Revised diagnostic criteria. J Med Genet 2000;37:828-30.
12. Ezgu MC, Ozer MI, Dogan A, Deveci G, Kural C, Izci Y. Lhermitte-Duclos disease in a six-year old child: A rare presentation. Pediatr Neurosurg 2018;53:416-20.
13. Farooq A, Walker LJ, Bowling J, Audisio RA. Cowden syndrome. Cancer Treat Rev 2010;36:577-83.
14. Georgescu MM. PTEN tumor suppressor network in PI3K-Akt pathway control. Genes Cancer 2010;1:1170-7.
15. Gharzeddine K, Hatzoglou V, Holodny AI, Young RJ. MR perfusion and MR spectroscopy of brain neoplasms. Radiol Clin North Am 2019;57:1177-88.
16. Han C, Zhang Y, Ran C, Luo Y, Li W. Diverse imaging findings of Lhermitte-Duclos disease. Clin Radiol 2023;78:33-9.
17. Hariri OR, Khachekian A, Muilli D, Amin J, Minassian T, Berman B, *et al.* Acute-onset cerebellar symptoms in Lhermitte-Duclos disease: Case report. Cerebellum 2013;12:127-30.
18. Iida S, Tanaka Y, Fujii H, Hayashi S, Kimura M, Nagareda T, *et al.* A heterozygous frameshift mutation of the PTEN/MMAC1 gene in a patient with Lhermitte-Duclos disease - only the mutated allele was expressed in the cerebellar tumor. Int J Mol Med 1998;1:925-9.
19. Jiang C, Lu WX, Yan GZ, Bai RB, Wang ZN, Chen Y, *et al.* Bilateral dysplastic gangliocytoma with concurrent polyostotic fibrous dysplasia: A case report and literature review. World Neurosurg 2020;141:421-4.
20. Jiang T, Wang J, Du J, Luo S, Liu R, Xie J, *et al.* Lhermitte-Duclos disease (dysplastic gangliocytoma of the cerebellum) and Cowden syndrome: Clinical experience from a single institution with long-term follow-up. World Neurosurg 2017;104:398-406.
21. Johnston JM, Limbrick DD, Ray WZ, Brown S, Shimony J, Park TS. Isolated cerebellar Rosai-Dorfman granuloma mimicking Lhermitte-Duclos disease. J Neurosurg Pediatr 2009;4:118-20.
22. Joo GJ, Doumanian J. Radiographic findings of dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease) in a woman with Cowden syndrome: A case study and literature review. J Radiol Case Rep 2020;14:1-6.
23. Khandpur U, Huntoon K, Smith-Cohn M, Shaw A, Elder JB. Bilateral recurrent dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease) in cowden syndrome: A case report and literature review. World Neurosurg 2019;127:319-25.
24. Kumar R, Vaid VK, Kalra SK. Lhermitte-Duclos disease. Childs Nerv Syst 2007;23:729-32.
25. Lhermitte J, Duclos P. Sur un ganglioneurome diffus du cortex du cervelet. Bull Assoc Franc Etude Cancer 1920;9:99-107.
26. Marano SR, Johnson PC, Spetzler RF. Recurrent Lhermitte-Duclos disease in a child. J Neurosurg 1988;69:599-603.

27. Nair P, Pal L, Jaiswal AK, Behari S. Lhermitte-Duclos disease associated with dysembryoplastic neuroepithelial tumor differentiation with characteristic magnetic resonance appearance of "tiger striping". World Neurosurg 2011;75:699-703.
28. Nowak DA, Trost HA, Porr A, Stölzle A, Lumenta CB. Lhermitte-Duclos disease (Dysplastic gangliocytoma of the cerebellum). Clin Neurol Neurosurg 2001;103:105-10.
29. Nowak DA, Trost HA. Lhermitte-Duclos disease (dysplastic cerebellar gangliocytoma): A malformation, hamartoma or neoplasm? Acta Neurol Scand 2002;105:137-45.
30. Pérez-Núñez A, Lagares A, Benítez J, Urioste M, Lobato RD, Ricoy JR, *et al.* Lhermitte-Duclos disease and Cowden disease: Clinical and genetic study in five patients with Lhermitte-Duclos disease and literature review. Acta Neurochir (Wien) 2004;146:679-90.
31. Pilarski R, Burt R, Kohlman W, Pho L, Shannon KM, Swisher E. Cowden syndrome and the PTEN hamartoma tumor syndrome: Systematic review and revised diagnostic criteria. J Natl Cancer Inst 2013;105:1607-16.
32. Pilarski R, Stephens JA, Noss R, Fisher JL, Prior TW. Predicting PTEN mutations: An evaluation of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome clinical features. J Med Genet 2011;48:505-12.
33. Pilarski R. PTEN hamartoma tumor syndrome: A clinical overview. Cancers (Basel) 2019;11:844.
34. Puri AS, Garg A, Mishra NK, Gaikwad SB, Mehta VS, Cirillo S. Bilateral cerebellar dysplastic gangliocytomas (Lhermitte Duclos disease) with cerebellar ectopia and presyrinx cord changes. Neuroradiol J 2006;19:717-21.
35. Reeder RF, Saunders RL, Roberts DW, Fratkin JD, Cromwell LD. Magnetic resonance imaging in the diagnosis and treatment of Lhermitte-Duclos disease (dysplastic gangliocytoma of the cerebellum). Neurosurgery 1988;23:240-5.
36. Robinson S, Cohen AR. Cowden disease and Lhermitte-Duclos disease: Characterization of a new phakomatosis. Neurosurgery 2000;46:371-83.
37. Robinson S, Cohen AR. Cowden disease and Lhermitte-Duclos disease: An update. Case report and review of the literature. Neurosurg Focus 2006;20:E6.
38. Sasongko TH, Ismail NF, Zabidi-Hussin Z. Rapamycin and rapalogs for tuberous sclerosis complex. Cochrane Database Syst Rev 2016;7:CD011272.
39. Shanley DJ, Vassallo CJ. Atypical presentation of Lhermitte-Duclos disease: Preoperative diagnosis with MRI. Neuroradiology 1992;34:103-4.
40. Shimanskiy VN, Karnaukhov VV, Shishkina LV, Vinogradov EV. The successful treatment of a patient with Lhermitte-Duclos disease (A case report and literature rewiew). Zh Vopr Neirokhir Im N N Burdenko 2015;79:78-83.
41. Sutphen R, Diamond TM, Minton SE, Peacocke M, Tsou HC, Root AW. Severe Lhermitte-Duclos disease with unique germline mutation of PTEN. Am J Med Genet 1999;82:290-3.
42. Tuli S, Provias JP, Bernstein M. Lhermitte-Duclos disease: Literature review and novel treatment strategy. Can J Neurol Sci 1997;24:155-60.
43. Vantomme N, Van Calenbergh F, Goffin J, Sciot R, Demaerel P, Plets C. Lhermitte-Duclos disease is a clinical manifestation of Cowden's syndrome. Surg Neurol 2001;56:201-4.
44. Verheggen R, Bruhn H, Schröder BU, Frahm J, Markakis E. Lhermitte-Duclos disease: A critical appraisal of different radiologic methods. Eur J Radiol 1994;19:21-4.
45. Vinchon M, Blond S, Lejeune JP, Krivosik I, Fossati P, Assaker R, *et al.* Association of Lhermitte-Duclos and Cowden disease: Report of a new case and review of the literature. J Neurol Neurosurg Psychiatry 1994;57:699-704.
46. Wang Q, Zhang S, Cheng J, Liu W, Hui X. Lhermitte-Duclos disease: Clinical study with long-term follow-up in a single institution. Clin Neurol Neurosurg 2017;162:53-8.
47. Xu L, Gao PY, Lin Y, Tian TD, Lei J, Ma L. Magnetic resonance imaging findings in Lhermitte-Duclos disease: Reports of three cases. Chin Med J (Engl) 2005;118:1933-6.
48. Zak M, Ledbetter M, Maertens P. Infantile Lhermitte-Duclos disease treated successfully with rapamycin. J Child Neurol 2017;32:322-6.
49. Zhang HW, Zhang YQ, Liu XL, Mo YQ, Lei Y, Lin F, *et al.* MR imaging features of Lhermitte-Duclos disease. Medicine (Baltimore) 2022;101:e28667.
50. Zhou XP, Marsh DJ, Morrison CD, Chaudhury AR, Maxwell M, Reifenberger G, *et al.* Germline inactivation of PTEN and dysregulation of the phosphoinositol-3-kinase/Akt pathway cause human Lhermitte-Duclos disease in adults. Am J Hum Genet 2003;73:1191-8.

How to cite this article: Alanazi AI, Alanezi T, Aljofan ZF, Alarabi A, Elwatidy S. Lhermitte–Duclos disease: A systematic review. Surg Neurol Int 2023;14:351.