

## CASE REPORT

## LHERMITTE-DUCLOS DISEASE: A RARE CEREBELLAR HAMARTOMA PRESENTING FOLLOWING TRAUMATIC BRAIN INJURY AND A REVIEW OF THE LITERATURE

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Lhermitte-Duclos Disease (LDD) is an extremely rare hamartoma of the cerebellum and is associated with the cancer syndrome Cowden's disease. We report such a patient whose disease was diagnosed incidental to traumatic brain injury. A 40-year-old male presented after fall from stairs. CT scan revealed a large lesion in the right cerebellar hemisphere. Clinical history recounted multiple short episodes of vomiting (>10 a week) for the past 30 years and development of posterior fossa symptoms over the recent months. Neither of these had him referred due to lack of access to primary healthcare. T1 MRI with contrast showed an isointense focal mass, enhancement along the folia, and distortion of the 4<sup>th</sup> ventricle. On T2 MRI, tiger striped appearance was noted. Endoscopic third ventriculostomy was performed followed by gross total resection of the hamartoma. Histology confirmed LDD. All reported symptoms resolved following surgery. Due to lack of access to the expensive genetic testing for Cowden's he is in regular biannual follow up to be evaluated clinically for associated malignancies. We present this case to highlight the clinical-pathological characteristics of LDD, its treatment, and discuss management in the absence of genetic testing in our socio-economic demographic.

**Keywords:** Lhermitte-Duclos Disease; Dysplastic Gangliocytoma; Cowden's Disease

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### INTRODUCTION

Hamartoma lesions anywhere in the body are considered rare entities, and Lhermitte-Duclos Disease (LDD) or dysplastic cerebellar gangliocytoma is an extremely rare hamartoma. It is a congenital malformation believed to be a hamartoma variety. Lhermitte-Duclos Disease arises in the cerebellum and is unique. Although it has characteristics of a benign neoplasm being categorized as a WHO grade 1 tumor,<sup>1</sup> histologically, it is more hamartomatous, containing dysplastic cells in an enlarged abnormal cerebellar folium.<sup>2</sup> It is now known that LDD is closely associated with Cowden's Disease, an autosomal dominant multiple hamartoma syndrome predisposing patients to malignancies.<sup>3</sup> Chromosome 10q23 mutations are considered the most widely reported aetiology of LDD<sup>4</sup> with granular cell migration and hypertrophy being shown to contribute to the disease's histogenesis.<sup>2</sup> The *PTEN* gene on chromosome 10 is implicated in both LDD and Cowden's. The germline mutations lead to a loss of inhibition of the phosphoinositide 3-kinase (PI3K) signal transduction

pathway, and subsequent activation of AKT/mTOR signalling contributes to the disease pathogenesis.<sup>4,5</sup> There is no gender preference, and whilst the disease is most commonly diagnosed in the second or third decade of life with posterior fossa symptoms,<sup>2</sup> sporadic cases in childhood-onset have also been reported.<sup>5</sup> A testament to the rarity of the disease is that less than 250 known cases of LDD have been published in PubMed indexed literature as of March 2020.<sup>6</sup> We discuss our encounter of such a case, in the setting of traumatic brain injury and highlight how in the developing world, these diseases are not caught or treated early and thus patients unduly suffer for a prolonged period of their life.

### CASE DESCRIPTION

A 40-year-old male presented at our surgical emergency after a history of fall from stairs due to dizziness followed by multiple vomiting and nasal bleed episodes. On examination, his presenting GCS was 14/15. He underwent CT brain, figure 1, and no significant finding regarding head injury was noted; however, a suspicious

mix density lesion in the right cerebellar hemisphere was noted with obstructive hydrocephalus. On detailed history, he revealed frequent episodes of dizziness and occipital headaches upon coughing, sneezing, and leaning forward, for the last three months and episodes of vomiting since age 10 which were brief but multiple attacks (more than 10) throughout the week. His clinical examination revealed cerebellar ataxia. Fundoscopic examination revealed papilledema Grade 3, visual acuity, fields, and colour visions were normal. Remaining history and examination were unremarkable. He recovered from his concussion and had an MRI brain with contrast, figure 2a, which affirmed a focal lesion with diffuse margin restricted to right cerebellar hemisphere appearing isointense on T1 and "tiger stripes" on T2 (Figure-3). T1 contrast MRI showed subtle enhancement along the folia. There was a distortion of the fourth ventricle along with compression on medulla oblongata and herniation of the cerebellar tonsils (Figure-2b).

The patient was admitted under trauma care to the Department of Neurosurgery and endoscopic third ventriculostomy (ETV) was done on the 15<sup>th</sup> post-admission day (Figure 4). One week later, he underwent right cerebellar lesion excision by paramedian suboccipital approach. Per operatively, the right cerebellar hemisphere was pale to greyish in colour with an enlarged and widened folium. The lesion was diffuse and moderately vascular with ill-defined margins. Gross total resection was achieved, and figure-5 shows the postoperative CT scan. Figure-6 shows the histopathology, the report of which documented intact cerebellar architecture with scattered dysplastic ganglion cells showing enlarged nuclei, prominent nucleoli, and abundant amorphous cytoplasm. Numerous ecstatic blood vessels are seen with surrounding areas of microcalcification. Axonal hypermyelination was noted, and there was no evidence of granuloma or malignancy in the biopsy. The postoperative course was uneventful; his headaches were relieved, vomiting episodes suppressed completely. He was discharged on the tenth postoperative day.

## DISCUSSION

Lhermitte-Duclos Disease is a very rare hamartomatous lesion. It is associated with Cowden's disease and is classed as a phakomatoses/ phacomatosis pigmentovascularis which encompasses rare disorders arising from embryonic ectoderm. These disorders have

a cutaneous and neurological involvement, often with dysplasia of other organs. The typical presentation includes cerebellar ataxia, lower cranial nerve palsies, signs, and symptoms of raised intracranial pressure and visual disturbances.<sup>2</sup> There is controversy on whether LDD constitutes a neurocytic blastoma, hamartoma or hyperplasia. The primary driving mutation identified for LDD is a germline loss of the *PTEN* allele and the subsequent loss of the second allele leading to pathological growth of the granular cells, additional mutations in the *EGFR*, and *SDHB-D* been reported.<sup>7,8</sup> Vomiting attacks are a unique presentation with only one case documenting what they described as rare pathophysiology of this cerebellar lesion, in which a patient had high-frequency vomiting attacks as the only main presenting symptom.<sup>8</sup> This was followed by the development of seizures which led to the diagnosis of epilepsy. It was only on re-evaluation and a new MRI that LDD was discovered. The lesion was fused with the middle and inferior cerebellar peduncles and the dorsolateral medulla oblongata.<sup>8</sup> Resection yielded complete suppression of the vomiting attacks, and the authors hypothesized that the lesion impacted the vomiting centre of the medulla oblongata. Such was the case for our patient and having isolated vomiting attacks throughout his life for 30 years which were never addressed due to lack of healthcare facilities in his area. Perhaps the lack of diagnosis is also the reason he was never misdiagnosed, and only when he suffered a traumatic brain injury from his fall and was referred to our centre in the city were we able to correlate his imaging to his clinical history and, fortunately, finally diagnose him with LDD. At that point, the lesion had evolved to cause posterior fossa symptoms in addition to his complaint of isolated vomiting attacks. He is free from his vomiting attack and other presenting symptoms. The complete remission of vomiting, he reports as the most significant improvement in his quality of life.

Due to the rarity of this disease, clinical diagnosis can be challenging, especially in our case wherein the setting of acute trauma, such a rare disorder would not even be considered on the list of differentials. Imaging, however, is crucial, and the typical appearance of 'tiger stripes' on T2 MRI can be pathognomonic for LDD. The lesion is described as focal, well-circumscribed isolated to a single cerebellar hemisphere with a characteristic gyri-form pattern and hypertrophy of the folia as the dysplastic ganglionic cells infiltrate and hypertrophy in the granular layer of the cerebellum.<sup>6,7</sup> MRI is very sensitive at detecting enlarged folia with T2 showing the characteristic 'tiger stripe' appearance, which is considered specific. The

histological specimen should be evaluated in conjunction with MRI and clinical information as histology alone, representing other ganglion cell tumours. Non-specific histological findings include dysplastic ganglion cells, microscopic expansion of granule cell layer, hypermyelination of molecular layers, calcification and mitosis.<sup>8</sup> Histology also is inconsistent with regards to the enlargement of the internal granular layer being inconspicuous and the relative preservation of the cerebellum's architecture reported to make histological evaluation difficult for pathologists as the infiltration of the molecular layer of the cerebellum needs to be differentiated from gliomas.<sup>9</sup>

Some authors have proposed that the 'tiger stripe' appearance on T2 MRI distinguishes LDD from cerebellar gliomas, which destroy the folia and thus the MRI is diagnostic without any need for further histological workup<sup>8</sup>; others suggest that histological workup is necessary as preoperatively they have misdiagnosed LDD as a medulloblastoma or a low-grade glioma.<sup>9</sup> Other diagnoses that may be suspected with such radiological presentation include nodular medulloblastoma in adults or pseudo tumoral hemisphericitis in children.<sup>6</sup> The former warrants gross resection with adjuvant therapy. The latter is a post-infectious inflammatory complication and is higher on the differential for children presenting with ataxia than LDD but regresses in terms of MRI findings over time.<sup>6</sup>

While LDD may be evident from T2 'tiger stripe' pattern, especially in developed countries where a genetic diagnosis of Cowden's syndrome is made or those who have hamartomatous cancer, we believe that those that have not been exposed to LDD in clinical practice or read about it with interest would be unlikely to include it on the differential even despite the unique 'tiger stripe' appearance. This was the situation with us, especially given the setting of acute trauma. As there is such little clinical data on this lesion, awareness of LDD is of utmost importance for neurosurgeons and radiologist. The former is most likely to encounter such isolated cases referred to them due to posterior fossa symptoms or MRI findings. Genetic testing for the overwhelming majority of the population is not available in Pakistan, an LMIC, even for common pathologies like cancer, let alone a disease as rare as LDD; therefore, in such a setting, most neurosurgeons would be evaluating such patients for the first time as the patients are unlikely to have undergone genetic testing in childhood or have the disease picked up early and hence serially monitored. With awareness comes clinical suspicion, which must be communicated with pathology colleagues to arrive at the correct diagnosis.

Histology alone, without clinical context, and MRI scan can be even more non-specific thus, both MRI and histology are necessary.

As LDD in and of itself is slow-growing, watchful waiting is recommended in asymptomatic patients. Only when the lesion grows large enough to cause posterior fossa symptoms is surgery performed.<sup>8</sup> Unfortunately, in Pakistan, genetic testing is non-existent for the masses, and primary healthcare is virtually lacking.<sup>10</sup> Thus, in an LMIC's circumstances, diseases that are generally slow-growing and asymptomatic, including but not limited to LDD, are only picked up when they advance enough to be symptomatic. This lack of primary care and secondary care<sup>4</sup> is, unfortunately, the reason why such patients are diagnosed late as hospitals with suitably qualified staff are only available in major teaching hospitals in the city, and thus referrals to these institutions are not made. In villages and rural districts, primary health and secondary care are extremely limited in the availability of qualified staff. MRI and even basic CT scan facilities are lacking. Our patients vomiting attacks alone did not get him a referral, and neither did his constellation of symptoms of dizziness, suboccipital headings, cough, and sneezing. Instead, it was his head injury that fortunately brought him to our attention to give him the care he needed.

There are two small case series but with long term follow up. Vantomme *et al.*<sup>8</sup> followed six patients with LDD, showing that 5 had clinical stigmata affecting various systems, including gynaecology, ophthalmology, neurology, general medicine, and dermatological findings suggestive of Cowden's disease. Only one patient, a five-year-old, did not have any apparent stigmata.<sup>8</sup> Wang *et al.*<sup>11</sup> followed 12 patients, and of these, 4 (33.3%) were diagnosed with Cowden's disease. The most commonly reported symptom for the presentation was raised intracranial pressure, with 9 out of 12 patients exhibiting tonsillar herniation and hydrocephalus, which was common to our case as well. The authors stated that gross total resection is difficult, only achieved in 3 out of the 12 patients (25%), partial resection in 6 patients (50%), and subtotal resection in 3 patients (25%).<sup>11</sup> We were, however, fortunate to have achieved a gross total resection. Rare recurrences have been documented by Wang *et al.* in 1 patient in their series of 12 in whom a gross total resection could not be achieved.<sup>11</sup> However, for Wang *et al.*, most of those who did not achieve a gross total resection had no recurrence over 13.5 years<sup>11</sup>; we believe the aim then should be maximum safe resection.

Breast and colon neoplasms are the most common tragedies in Cowden's patients. These are the most commonly investigated for cancers, and genetic testing is warranted.<sup>12</sup> Unfortunately, our patient, like most others in our setting, was non-affording and as genetic testing for Cowden's is not available in public sector hospitals, nor could the patient afford it privately, we have informed him of the possible association and the need for constant follow up which we have referred him for to our internal medicine department. He was assessed, and there were no clinical stigmata of Cowden's disease. Most recently, 6 months following discharge, he was assessed, and there were no clinical stigmata of Cowden's disease and follow-up was unremarkable.

The patient is advised for at least biannual follow-up. We summarise in table-1, adapted from Mester *et al.* 2014,<sup>13</sup> the malignancies for which should be evaluated for in patients who may have Cowden's and it is these that our patient is clinically evaluated for by our medicine colleagues. Lhermitte-Duclos Disease is of the major diagnostic criteria, but diagnosis requires two or more major criteria of which one must be either LDD or macrocephaly. Our patient did not have the pathognomonic criteria (any of which would be diagnostic for Cowden's) which includes >6 facial papules with biopsy confirmed trichilemmomas in 3, oral mucosal papillomatosis, or mucosal papillomatosis with acral keratoses. The minor criteria is also summarised in table 1 and can be diagnostic if there is 4 minor criteria present, or one major plus 3 minor.<sup>13</sup>

## CONCLUSION

We present a case of LDD diagnosed incidentally in a patient presenting following traumatic brain injury. LDD is a rare hamartomatous lesion of the cerebellar hemisphere. When the lesion goes undiagnosed and treatment is delayed, the hamartoma can grow large, compress the brain, cause mass effect and raised intracranial pressure thus warrants surgical excision. LDD is associated with obstructive hydrocephalus, which can be life-threatening. Neurosurgeons and radiologists should be aware of T2 'tiger stripe' appearance to raise suspicion for LDD and investigate such patients for Cowden's disease where possible. When LDD is diagnosed, workup for Cowden's disease is imperative for future management. But in the absence of genetic testing, these individuals should be clinically monitored for malignancies discussed given the high incidence of cancer of various systems in Cowden's cancer syndrome.

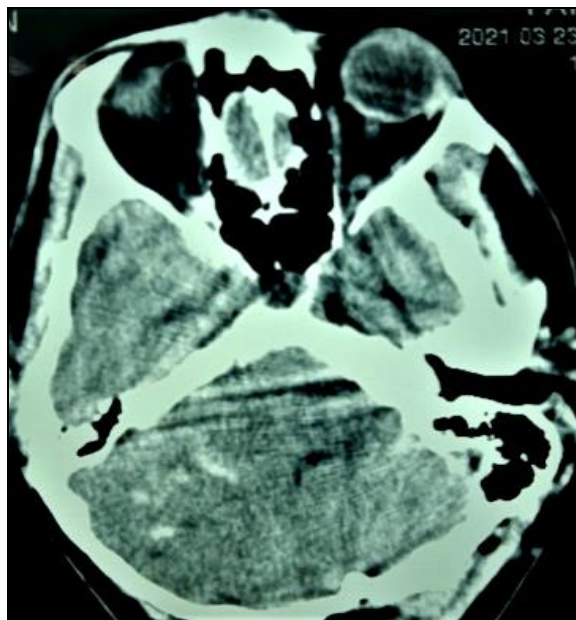


Figure-1: Preoperative CT Scan

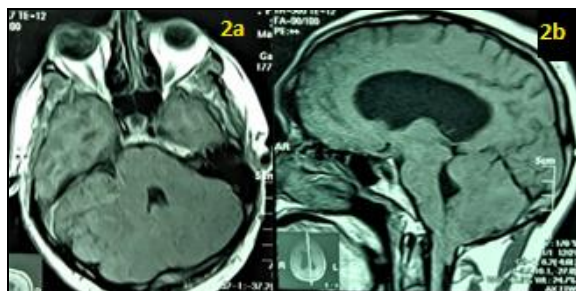


Figure-2: 2a Axial T1 MRI with contrast; 2b T1 MRI with contrast sagittal showing tonsillar herniation



Figure-3: T2 MRI showing classic 'tiger striped' appearance of Lhermitte-Duclos disease





Figure-4: Endoscopic third ventriculostomy

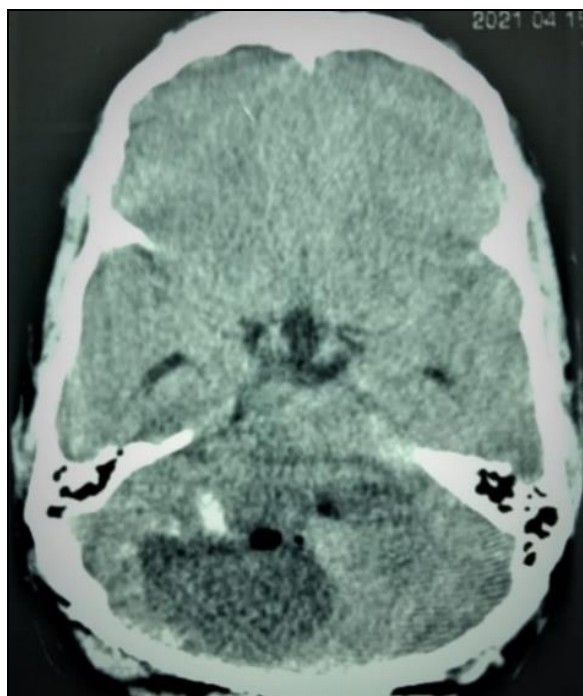


Figure-5: Post resection CT scan

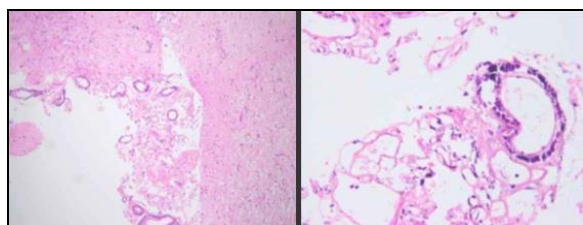


Figure-6: Dysplastic ganglion cells with axonal hypermyelination

Table-1 (Adapted from Mester *et al.* 2014<sup>15</sup>) illustrates the associated diseases for Cowden's

syndrome. Malignancies and diseases are stratified by the likelihood of association with Cowden's disease and provide a framework for clinical suspicion which can be useful in the absence of genetic testing.

Pathognomonic Malignancies and Diseases	Major Associated Malignancies and Diseases	Minor Associated Malignancy and Diseases
Acral Keratoses Mucosal Lesions Facial trichilemmomas Papillomatous papules	Breast Cancer <b>Lhermitte-Duclos Disease</b> Macrocephaly Endometrium Cancer Thyroid Carcinoma (excluding-medullary)	Benign thyroid lesions Hamartomatous polyps of the intestinal tract. Lipomas and Fibromas Fibrocystic Breast Genital-urinary tract malformations and tumours

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