

## Dysplastic Gangliocytoma of the Cerebellum: A Case of Cerebellar Lesion, Finally Diagnosed Five Years Later

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### ABSTRACT

Dysplastic Gangliocytoma of the Cerebellum, also called as Lhermitte-Duclos Disease (LDD), is a rare condition. The importance of diagnosing it is to rule out co-existent Cowden's syndrome by thorough clinical examination in view of increased risk of visceral malignancy associated with the latter. Though considered as hamartomatous lesion by some, it is mentioned as a tumour of central nervous system by WHO (Grade I). A lesion, seen in young adults usually, presents with signs & symptoms of raised intracranial tension. We herein describe a case that came with the symptoms of obstructive hydrocephalus five years back and diagnosed as having some tiny cerebellar lesion on imaging. As the patient was not willing to have biopsy done for definitive diagnosis at that time, it remained undiscovered till present. This time, classical MRI finding (tiger stripes appearance) & diagnostic histopathological features were seen leading to the diagnosis. Association with Cowden's syndrome was not found in this case.

**Keywords:** *Dysplastic Gangliocytoma, Lhermitte-Duclos Disease, Cowden's syndrome.*

### Introduction

Dysplastic Gangliocytoma of the Cerebellum which is also called as Lhermitte-Duclos Disease was first described by Lhermitte and Duclos in 1920.<sup>[1]</sup> It is a rare condition with fewer than 220 cases reported till date. Many of the cases are part of Cowden's Syndrome. It is considered by some as hamartomatous lesion, but still finds its place in tumours of central nervous system.<sup>[2]</sup> It is seen most commonly in young adults i.e. third or fourth decade of life,<sup>[3]</sup> fewer are documented in children. This case reports of a patient who presented with signs & symptoms of raised intracranial tension, was later diagnosed as a case of Dysplastic Cerebellar Gangliocytoma.

### Case Report

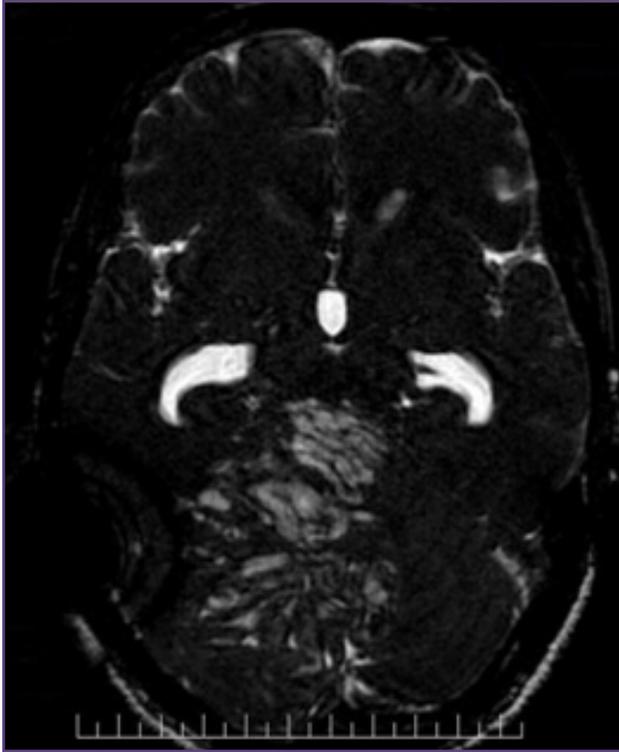
A 36 years old male patient presented 5 years back with complaints of irritability, unstable gait, tendency to injure himself & slurred speech for 6 months. Sudden onset of headache, vomiting and altered sensorium caused him to be brought to casualty for which he was investigated. He was diagnosed as having some tiny cerebellar lesion with obstructive hydrocephalus, the reports of which are not available with them at present. Placement of Ventriculo Peritoneal shunt was done to relieve the symptoms of increased intracranial pressure. Patient was not willing for subsequent biopsy of cerebellar lesion. Though close follow up was advised, but he didn't turn up later. After 5 years this patient came again complaining recurrence of the same symptoms since 8 months, with worsening of these

and severe headache since 2 days. No history of vomiting and seizures was there. Neurological examination revealed an unsteady gait with impaired finger - nose - finger test. Laboratory blood investigations were within normal limits. MRI scan of brain showed VP shunt in situ; along with a 8x4x6 cm striated lesion showing non-enhancing, classical alternate iso & hypo intense bands in right cerebellar hemisphere, vermis & right cerebellar peduncle causing significant compression onto the fourth ventricle, bulging into the quadrigeminal cistern on T2W1 image (Fig 1). Patient underwent right suboccipital craniotomy with right cerebellar tumour excision, which was submitted for histopathological examination. Multiple soft bits were received aggregating about 3x3x0.5 cm. Histologically the section showed enlarged, thickened cerebellar folia.

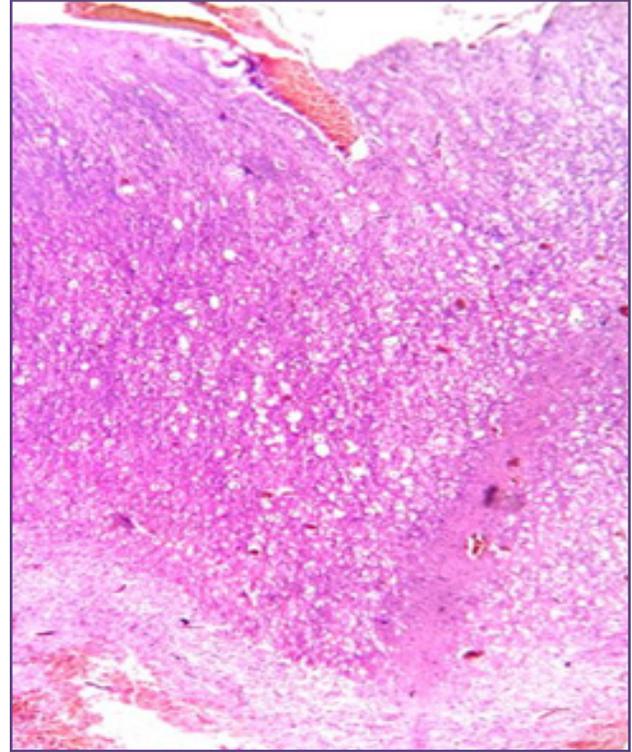
The molecular and internal granular layers were diffusely enlarged (Fig 2), with the internal granular layer (IGL) being replaced by large, varying sized neurons with eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli. Also seen were dysplastic ganglion cells in IGL, with central to eccentric, round nuclei with finely granular chromatin and occasionally prominent nucleoli and nucleomegaly (Fig 3). Purkinje cells were not seen throughout the sections. The molecular layer showed thickened and elongated axonal bundles. Artefactual vacuolization was prominently noted in molecular layers and white matter, which may have given rise to prominent stripes in MRI images. No mitoses were found. Dysplastic cerebellar

gangliocytoma WHO grade I (Lhermitte-Duclos disease) was given as final diagnosis considering radiological features. As the classical and unique MRI findings of LDD correlated with histopathology, tissue was not subjected

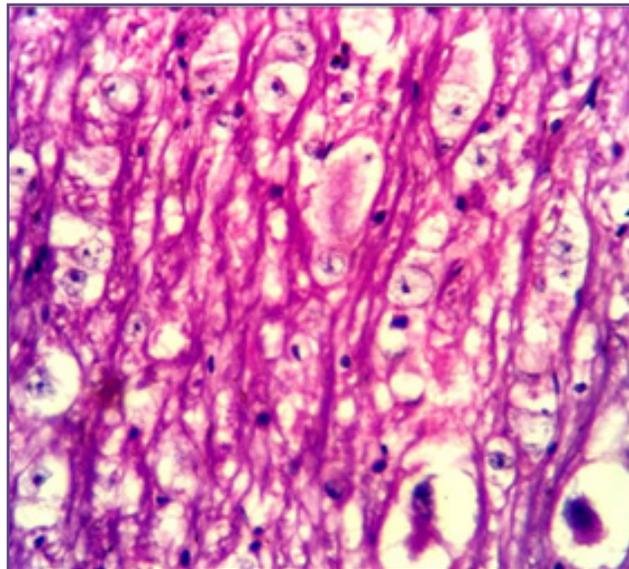
to Immunohistochemistry. Post-operatively patient was relieved of neurological symptoms with uneventful course. Thorough work up was done and Cowden syndrome was ruled out.



**Fig. 1:** Characteristic "Tiger striped pattern" or striated appearance with alternate strips of hypo and hyperintensities in the right cerebellar hemisphere on T2Weighted MR image.



**Fig. 2:** Diffusely enlarged molecular and internal granular layers. (HE, 40X).



**Fig. 3:** Dysplastic ganglion cells. (HE, 400X).

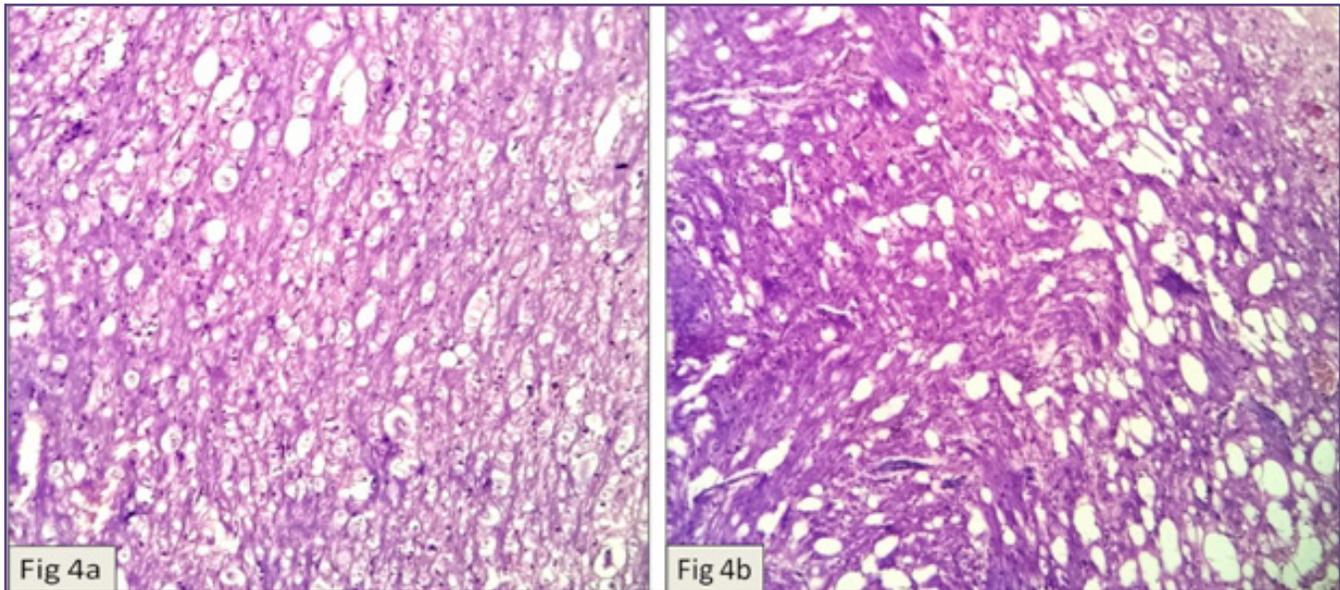


Fig. 4 a &b: Artefactual vacuolization in molecular layers. (HE, 100x).

## Discussion

Jacques Jean Lhermitte and P. Duclos first described this rare, slowly growing lesion of the cerebellum in 1920.<sup>[1]</sup> The incidence is very less, 5 per million per year and approximately 222 cases of LDD have been reported in medical literature till now.<sup>[4]</sup> The age of onset of symptoms may be at any, but most commonly manifests in the third and fourth decades of life.<sup>[5]</sup> There is neither gender predilection & nor any apparent geographical pattern.<sup>[5]</sup> The lesion is typically unilateral, usually found on the left cerebellar hemisphere. This case had lesion on right side instead. There are plenty of alternate names for this condition as purkinjinoma, hamartoma of cerebellum, diffuse ganglioneuroma of cerebellar cortex, benign hypertrophy of cerebellum, neurocystic blastoma, hamartoblastoma, gangliomatosis of the cerebellum, Lhermitte-Duclos disease, neurocytoma myelinicum, and gangliocytoma myelinicum diffusum. As this indicates, still there is confusion whether LDD is hamartomatous or neoplastic. Neoplastic nature is suggested by its position in tumours of central nervous system,<sup>2</sup> corresponding to WHO Grade I. Also, occurrence in adults with previous normal MRI and recurrence in occasional cases, point towards the same. Cerebellar granule neuron is the cell of origin. Combination of its aberrant migration & hypertrophy is responsible for its development.<sup>[6]</sup> However, malformative histopathological features, absent proliferative activity and absence of progression favour hamartomatous origin.

The pathogenesis has been clarified by the linking of these lesions in adulthood to *PTEN* (*Phosphatase Ten sin homologue on chromosome TEN*) gene mutation, which

is reported in high frequency in these cases.<sup>[7]</sup> *PTEN* has inhibitory action on the phosphatidylinositol 3-kinase (PI3K)/AKT signaling cascade, and through this it has role in regulation of cell size, survival, proliferation, and migration. Studies suggest that abrogated *PTEN* expression result in activation of AKT and its downstream targets, ultimately producing the characteristic alterations of dysplastic cerebellar gangliocytomas in the absence of transforming events or cellular proliferation.<sup>[6], [8-9]</sup> This is represented by a compensatory hypertrophy of internal granule cells in response to faulty development of the fetal external granular layer from which they are derived.

Clinical picture is presented as asymptomatic lesion (examination found) or symptoms are due to mass effect in the posterior cranial fossa, consequent hydrocephalus (the 4th ventricle compression), progressive cerebellar dysfunction and increased intracranial pressure.<sup>[10]</sup> The duration of symptoms is variable, ranging from a few months to over 10 years. In our case it was 5 1/2 years. Malformation such macrocephaly, megacephaly, syringomyelia, polydactyly, multiple haemangiomas and mucocutaneous lesions as well as breast, thyroid, genitourinary and gastrointestinal malignancies are often associated with it.<sup>[11]</sup> A genetic correlation between LDD and Cowden's syndrome, an autosomal dominant syndrome characterised by germline mutations of the *PTEN/MMAC1* gene on chromosome 10q23 and multiple hamartomas and tumors of endodermal origin, mesodermal and ectodermal has been found. About 40% of cerebellar dysplastic gangliocytoma occur as part of Cowden disease.<sup>[12]</sup> When the dysplastic gangliocytoma is adult-onset, it is

recognized as a lesion virtually pathognomonic of Cowden syndrome.<sup>[13]</sup> Our patient had solitary LDD.

On CT scan, the lesion of Lhermitte-Duclos disease appears as hypodense non-enhancing mass in cerebellar hemisphere with enhancing and thickened folia. An avascular lesion is seen on angiography. MRI is the imaging test of choice which will feature a non-enhancing cerebellar mass with a typical alternate iso and hyperintense thickened folia “Tiger striped pattern” or striated appearance on T2W images.<sup>[6, 18]</sup> Also, when compared with CT, MRI depicts the extent of LDD in a clearly superior manner. Establishing preoperative diagnosis of LDD with MRI obviates the need for biopsy and this allows neurosurgeons to plan for appropriate treatment.

Grossly the lesion appears poorly circumscribed mass showing thickened, enlarged, firm gyri in contrast to the adjacent normal appearing folia. On histology normally the cortex (skin or rind) of a folium consists of three layers of cells - the outer(top) molecular layer, the Purkinje layer, and the inner (bottom) granular layer - and this cortex covers deeper white matter (interconnecting fibers). In this condition the enlarged folia shows two layer pattern. The inner granular layer is replaced by large neurons resembling ganglion cells. The outer molecular layer shows thickened and myelinated axonal bundles. The Purkinje cell layer is absent. The molecular layer may also show microcystic change & calcific blood vessels. In a fragmented biopsy when architecture is not very clear, the radiological features will help in clinching the correct diagnosis.

The differential diagnoses are conventional ganglion cell tumors: gangliocytoma & ganglioglioma. Classical radiological features along with geographic confinement of ganglion cells to internal granular layer favor the diagnosis of LDD; while in conventional gangliocytoma & ganglioglioma, irregular distribution of variable sized neurons of ganglion cell type are seen against a background of delicate fibrillary matrix. Also, the later are more cellular and distinct mass lesions. In case of ganglioglioma, glial component is typically astrocytic and GFAP positive.<sup>[14]</sup> Differential imaging considerations; including hemangioblastoma, glial tumor, diffuse astrocytoma, desmoplastic medulloblastoma, primitive neuroectodermal tumor, subacute infarct, cerebellitis, or tumefactive demyelination; are limited by the pathognomonic appearance on MRI.<sup>[15]</sup>

Despite the benign nature of the lesion, surgical excision is the treatment of choice for large lesions with mass effect on ventricles, although most centres may prefer conservative management in asymptomatic cases. Decompression of ventricular system is the immediate goal of therapy in

virtually all cases. A ventricular shunt is placed initially followed by tumor resection. The precise margin of abnormal tissue of this tumor should be assessed under surgical microscope since well defined border of lesion seen on MRI is not always apparent during surgical exploration. Similarly, total resection may not be possible in all cases as clear cut demarcation between lesion & surrounding normal brain parenchyma is usually not found intraoperatively. It may be the cause for recurrence noted in some cases. Long-term follow-up is indicated, as recurrence of up to 20 years has been reported after surgical resection.<sup>[10]</sup> Radiation therapy is ineffective.

## Conclusion

To conclude, dysplastic cerebellar gangliocytoma is a rare lesion of posterior cranial fossa with benign behaviour. Whether classical tiger stripes appearance is seen in MRI images or not, the patient presenting with symptoms of cerebellar tumor and significant cerebellar mass effect on CT scan should be managed with surgical removal. The histopathological features in themselves are also diagnostic. The importance of diagnosing this condition is to rule out co-existent Cowden’s syndrome by thorough clinical examination in view of increased risk of visceral malignancy.

## Reference

1. Lhermitte J, Duclos P. Sur un ganglioneuroma diffus du cortex du cervelet. *Bull Assoc Franc Cancer.* 1920; 9: 99-107.
2. Louis DN, Perry A, Reifenberger G et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol.* 2016; 131: 803–820.
3. Nowak DA, Trost HA. Lhermitte-Duclos disease (dysplastic cerebellar gangliocytoma): a malformation, hamartoma or neoplasm? *Acta Neurol Scand.* 2002; 105: 137-45.
4. Robinson S, Cohen AR. Cowden disease and Lhermitte-Duclos disease: an update. Case report and review of the literature. *Neurosurg Focus.* 2006; 20 (1): E6.
5. Kumar R, Vaid VK, Kalra SK. Lhermitte-Duclos disease. *Child’s Nervous System.* 2007; 23 (7): 729–32.
6. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. WHO classification of tumors of central nervous system. 4th ed. Lyon: IARC; 2007.
7. Chiofalo MG, Cappabianca P, Basso De Caro MLD, Pezzullo L. Lhermitte – Duclos Disease. *J Neurooncol.* 2007; 82: 183-185.
8. Abel TW, Baker SJ, Fraser MM et al. Lhermitte–Duclos disease: a report of 31 cases with immunohistochemical analysis of the PTEN/AKT/mTOR pathway. *J Neuropathol Exp Neurol.* 2005; 64:341-349.

9. Zhou XP, Marsh DJ, Morrison CD 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; 73:1191-1198.
10. Shingare AB, Patil NK, Sorte SZ. Dysplastic gangliocytoma of the cerebellum. *Radiology.* 2009; 251: 298-303.
11. Koeller KK, Henry JM.) Superficial Gliomas: Radiologic-Pathologic Correlation. *Radiographics.* 2001; 21: 1533-1556.
12. Murray C, Shipman P, Khangure M et al. Lhermitte-Duclos Disease. *Australasian Radiology.* 2001; 45, 343-346.
13. Eberhart CG, Wiestler OD, Eng C. Cowden disease and dysplastic gangliocytoma of the cerebellum/Lhermitte–Duclos disease. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. *WHO classification of tumours of the central nervous system.* 4th ed Lyon: IARC; 2007:113-114.
14. Rosenblum MK. Chapter 28 Central nervous system. In: Juan Rosai. *Rosai & Ackerman’s Surgical Pathology.* 10th ed. New York: Elsevier; 2012: 2367.
15. Rheinboldt M, Delproposto Z, Blasé J, Hakim B. Acute presentation of Lhermitte-Duclos disease in an adult patient in association with Cowden syndrome. *Appl Radiol.* 2016; 45(8): 28-31.

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