

# Lhermitte-Duclos Disease and Cowden's Syndrome: Importance of the Clinical Association

## Lhermitte-Duclos Hastalığı ve Cowden Sendromu: Klinik Birlikteliğin Önemi

### ABSTRACT

Lhermitte-Duclos disease is a rare hamartomatous lesion of the cerebellar cortex that may occur in the setting of Cowden's syndrome, an autosomal dominant condition characterised by multiple hamartomas and neoplastic lesions in skin and internal organs. We add a further case to this rare entity. A 55-year-old female presented with a 3-month history of progressive headaches occasionally associated with nausea and vomiting. Magnetic resonance imaging revealed the presence of a well-defined lesion with an abnormal laminated pattern of cortical architecture involving most of the left cerebellar hemisphere and compressing the fourth ventricle. Complete removal of the cerebellar lesion was performed and histopathological diagnosis verified Lhermitte-Duclos disease. The associated skin lesions and the patients past history of tumors were sufficient for the final diagnosis of Cowden's syndrome. Accurate preoperative diagnosis of Lhermitte-Duclos disease can be made on the characteristic magnetic resonance imaging appearances. It is important to be aware of the link between Lhermitte-Duclos disease and Cowden's syndrome so that appropriate tumor surveillance can be undertaken by the treating physician.

**KEY WORDS:** Lhermitte-Duclos disease, Dysplastic gangliocytoma, Cowden's syndrome

### ÖZ

Lhermitte-Duclos Hastalığı serebellar korteksin nadir görülen hamartamatöz bir lezyonu olup, cilt ve iç organların neoplazik lezyonları ve multipl hamartomaları ile karakterize otozomal dominant bir tablo olan Cowden Sendromu içerisinde ortaya çıkabilir. Biz bu nadir sendroma bir olgu daha ekliyoruz. 55 yaşında kadın hasta aralıklarla bulantı ve kusmanın da eşlik ettiği 3 aydır devam eden ilerleyen başağrısı şikayeti ile başvurdu. Magnetik rezonans görüntüleme ile dördüncü ventriküle bası yapan ve sol cerebellar hemisferin büyük kısmını içine alan kortikal yapının anormal laminizasyon paterni gösteren iyi sınırlı bir lezyon belirlendi. Cerebellar lezyon total olarak çıkarıldı ve histopatolojik olarak Lhermitte-Duclos Hastalığı tanısı doğrulandı. Eşlik eden cilt lezyonları ve hastanın tümörleri ile ilgili olan özgeçmiş Cowden Sendromu tanısının konmasında yeterli oldu. Lhermitte-Duclos hastalığının doğru preoperatif tanısı karakteristik manyetik rezonans görüntüleme bulguları ile konabilir. Lhermitte-Duclos hastalığı ve Cowden Sendromu arasındaki bağlantının farkında olmak tedavi eden hekimin uygun bir şekilde tümör takibi yapabilmesi açısından önemlidir.

**ANAHTAR SÖZCÜKLER:** Lhermitte-Duclos Hastalığı, Displastik gangliositoma, Cowden Sendromu

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## INTRODUCTION

Lhermitte-Duclos disease (LDD) is a rare pathological entity, first described in 1920 (7). It is characterised by a slowly enlarging mass within the cerebellar cortex. The origin and nature of the lesion and whether it is neoplastic, malformative or hamartomatous is still not exactly understood. Patients frequently present with signs of intracranial pressure or cerebellar dysfunction.

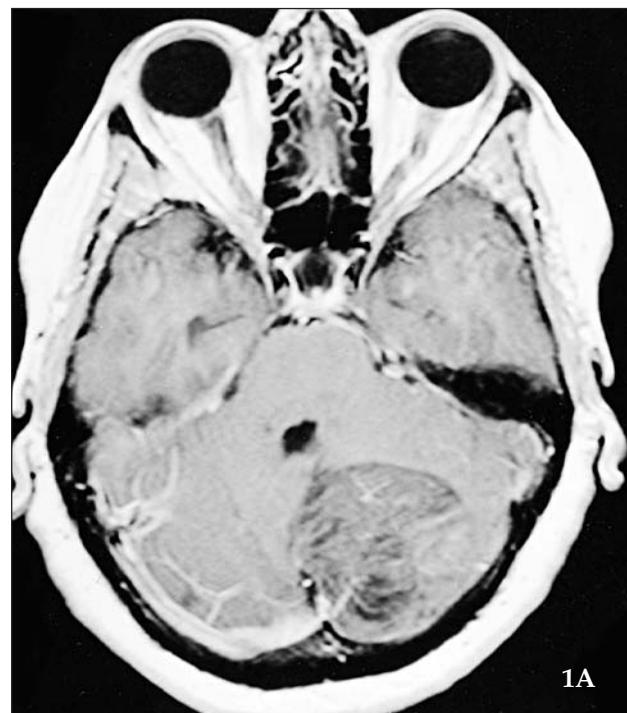
Cowden's syndrome (CS), also called "multiple hamartoma-neoplasia syndrome", is an unusual autosomal dominant disorder characterized by mucocutaneous lesions, systemic hamartomas, and a high incidence of breast thyroid, genito-urinary, and endometrial cancers (12). Padberg et al. described the association between CS and LDD in 1991 (14). Only a few cases of coexisting LDD and CS have been reported since then (13, 16, 23, 24). This association still remains relatively unknown in the neurosurgical community but it is important because of the premalignant nature of CS.

We present a case of LDD in whom CS had never been suspected until the diagnosis of LDD was made, although the medical history of multinodular goiter, endometrial carcinoma and mucocutaneous lesions were highly suggestive for CS.

## CASE REPORT

A 55-year-old female presented with a 3-month history of progressive headaches occasionally associated with nausea and vomiting. Her medical history included a hysterectomy for endometrial carcinoma 6 years ago and multinodular goiter operation at the age of 18. Her mother had undergone a mastectomy for the treatment of a breast cancer. The rest of the family history was unremarkable for any cancer or neurocutaneous condition and she appeared to be free of neurological deficits except a slightly ataxic gait.

Magnetic resonance imaging (MRI) revealed the presence of a well-defined lesion with an abnormal laminated pattern of cortical architecture involving most of the left cerebellar hemisphere and compressing the fourth ventricle (Figures 1A, B, C). The lesion was hypointense on T1-weighted images and hyperintense on T2-weighted images. There was only laminar thin enhancement with intravenous contrast agents. No obvious vasogenic oedema was found around the mass. The lateral ventricles were normal, and the cerebellar tonsils were herniated downward.

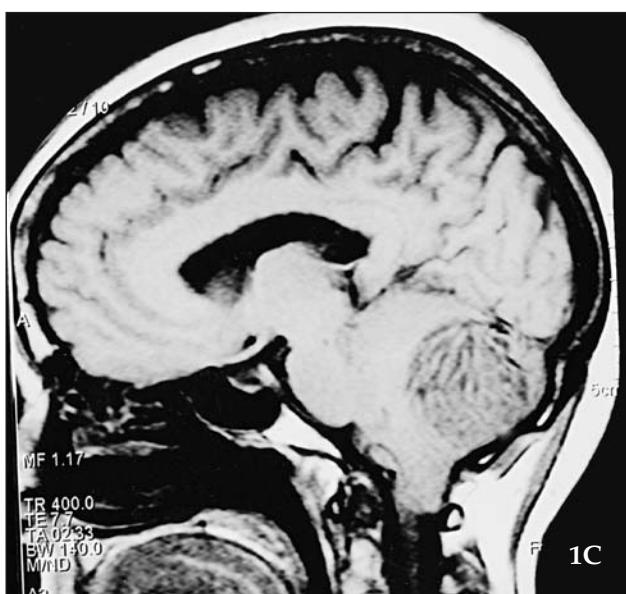


1A



1B

**Figure 1A, B, C :** Typical magnetic resonance image (MRI) findings of Lhermitte-Duclos disease. (A) T1-weighted axial image following administration of Gd-DTPA demonstrates alternating layers of T1 isointensity and hypointensity creating a mass effect. There is only laminar thin contrast enhancement. (B) T2-weighted coronal MRI. The lesion is characterised by a well-circumscribed hyperintensity and a typical striped pattern with lamellar areas of isointensity within the region of hyperintensity. No obvious vasogenic oedema is seen around the mass. (C) Sagittal T1-weighted image demonstrating the distinct tiger-striped appearance with abnormally oriented folia.

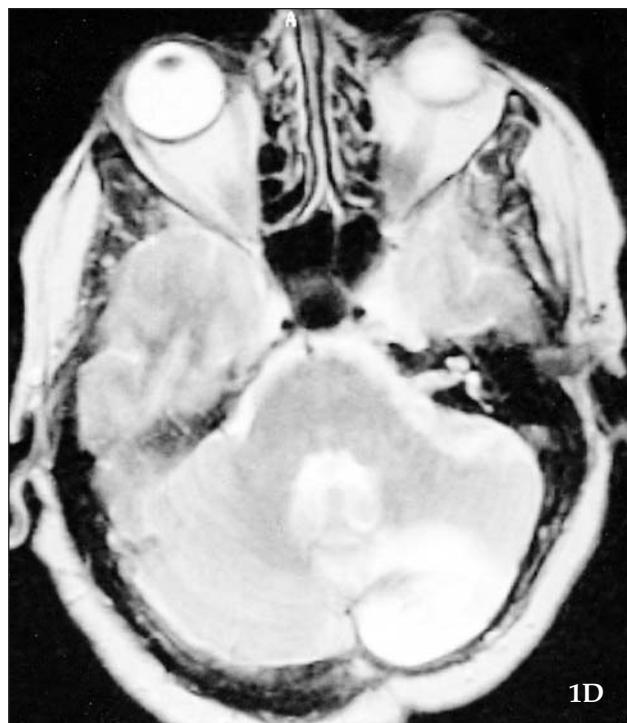


A confident diagnosis of LDD was made on the basis of the MRI findings. A left lateral suboccipital craniectomy allowed total resection of the tumour, which appeared as thickened folia with a yellowish white surface mimicking cerebellar cortex. The tumour consistency was the same of the cerebellar tissue, and a clear demarcation of the pathologic tissue was found only at the cerebellar cortex. At the deep areas, the lesion blended into normal cerebellar tissue. The radiological laminar pattern of the lesion was also evident intraoperatively, and although the lesion blended into normal cerebellar tissue, gentle tractions of the thickened folias permitted detachment of these lamellas from the cerebellum at the deep areas of the tumour. Feeding arteries of the mass were evident only at the tentorial and medial side of the tumour.

On histopathological examination the folia showed thickened architecture. The sections of the folium that were composed of disorganized small and large neuronal cells had mature features. There were normal cerebellar cortical areas between the dysplastic neuronal areas. The dysplastic neuronal cells were stained positive for synaptophysin and chromogranin but not for glial fibrillary acidic protein. The score of Ki-67 was less than 1%; only a few cells showed Ki-67 positivity and mitotic activity was not observed in these cells. These findings were consistent with LDD.

The postoperative course was uneventful. The headaches and ataxic gait resolved early after the surgery and she was hospitalized in the Department

of Internal Medicine for further clinical examination. Dermatological consultation revealed small fleshy keratoses on the dorsum of the hands, gingival hyperplasia and tongue papules. Thyroid study, mammography, and gynaecological and ophthalmologic examination results were normal. Chromosome analysis showed a normal female karyotype. A final diagnosis of CS was made in light of the patient's past history, cerebellar lesion and dermatological findings. Control MRI scans 3 months after surgery revealed no residual lesion (Figure 1D).



**Figure 1D:** No residual lesion is seen on post-operative T2-weighted axial MRI.

## DISCUSSION

LDD differ significantly from other mass lesion of the cerebellum by its uncommon pathological and radiological findings, and by its strong association with CS. The exact nature of this lesion is unclear, but it has been considered as a hypertrophy, a hamartoma, or a benign neoplasm, which accounts for the various nomenclatures for this abnormality, such as hamartoma of the cerebellum, hamartoblastoma, granule cell hypertrophy, diffuse ganglioneuroma of the cerebellar cortex, gangliocytoma myelinicum, myelinated neurocytoma, and Purkinjeoma (6).

Patients with LDD commonly present with a long-standing history of vague defined neurological symptoms, usually related to increased intracranial pressure and hydrocephalus, followed by cerebellar signs and cranial nerve deficits (13, 16, 23, 24). Severe orthostatic hypotension (18) and acute subarachnoid haemorrhage (22) are atypical clinical manifestations. Most frequently, patients become symptomatic during the third to fourth decades of life (13, 16, 23, 24). Cases of LDD also occur in paediatric patients (2, 9, 17). In one series by Ambler et al. (1), the average age was 34 years. Those authors described the first familial association and possible dominant mode of transmission of the disease in a mother and son, although no additional cases of suspected genetic association have been reported.

In 1991, Padberg et al. (14) described the association between LDD and CS. They stated that LDD and CS are a single phakomatosis. CS, also called "multiple hamartoma-neoplasia syndrome", is an autosomal dominant disorder, defined by the association of cutaneous and oral tricholemmomas, with dysmorphic anomalies including craniomegaly, adenoid facies, high-arched plate, kyphosis and a propensity to develop tumours of the skin, breast, thyroid, or gastrointestinal tract (23, 24). The diagnosis of CS has been clarified by an international consortium (12). In the presence of LDD, the diagnosis criteria for CS are fulfilled if one other major manifestation of CS or three minor criteria are present. In our case, the diagnosis of CS is suggested most strongly by the history of endometrial carcinoma and multinodular goitre coexisting with the patient's dermatologic signs. In 1996, Nelen et al. (12) localized the gene for CS to chromosome 10q22-23. This susceptibility gene was designated PTEN by Li et al. in 1997 (8). PTEN is a powerful tumour suppressor gene with diverse biological functions. It affects all three primary modes of tumour progression, that is, cell division, survival, and migration (16).

Macroscopically, LDD represents a focally indolent growth of the cerebellar cortex resulting in gross thickening of the cerebellar folia. The enlarged folia lose their secondary folding and asymmetrically expand the cerebellar hemisphere. The disease is typically unilateral with a predilection for the left cerebellar hemisphere (11). Histologically, LDD is characterized by a thickening of the

outermost molecular layer and replacement of the innermost Purkinje and granular cell layer with a profusion of dysplastic ganglion cells. Mitoses, neovascularity and necrosis are not observed, emphasizing the presumed hamartomatous nature of the lesion.

The diagnosis of LDD was, until recently, made post-operatively or on autopsy. However, morphological changes produce a unique pattern on MRI, allowing a preoperative diagnosis by the radiologist (3). The first diagnostic magnetic resonance images of this condition were reported in the literature in 1988 (19). On MRI, Lhermitte-Duclos lesions are hypointense on T1 weighted images and show few or no enhancement following injection of Gd-DTPA, suggesting insignificant disturbances of the blood-brain-barrier and/or extra-cellular oedema. Spaargaren et al. suggested that peripheral enhancement of LDD reflects vascular proliferation of the cerebellar venous drainage system (21). On T2-weighted images, the lesion presents with a well-circumscribed high-signal intensity and a unique striated pattern with isointense bands within the area of hyperintensity, indicating the structures of enlarged gyri and compressed sulci of the cerebellar cortex (10). Occasionally, this unique foliation of LDD may be difficult to detect on T1-weighted images as a result of its homogeneous appearance (20). However, our case had areas of extreme hypointensity on T1-weighted scans. This unique parallel linear striation has been likened to a "tiger-stripe" appearance.

Outcome in patients not treated surgically was uniformly poor for early cases, obviously due to the progressive enlargement of the growing tumour process (1, 3). However, long symptomatic periods over several years until massive clinical deterioration (1, 3, 16), and incidental recognition of dysplastic cerebellar gangliocytoma at autopsy (4, 15) in asymptomatic patients suggest slow growth of the tumour tissue. Surgery is the treatment of choice (3, 16). Recurrences several years following tumour resection have been described (3, 9), but Lhermitte-Duclos lesions exhibit no proliferative growth potential as determined by immunohistochemical analysis with monoclonal antibodies to cell nuclear antigens (as performed in our case with the Ki-67 antibody) and measurements of proliferation indices (5). The lesion usually blends into normal cerebellar tissue and complete tumour resection was attempted only with a good delineation of the limits of the

lesion on MRI. After this stage, the lesion removal is safe because the laminar patterns of the lesion are easily detachable from the cerebellum. A suboccipital approach is the surgical procedure generally performed and additional permanent ventricular shunting occasionally precedes or follows tumour resection (9, 13, 16).

### CONCLUSION

The characteristic striated appearance of the cerebellar lesion (hypointense on T1- and hyperintense on T2-weighted MR images) without apparent contrast enhancement on MRI is highly suggestive of LDD. MRI will greatly assist the surgical approach by defining the extent of the disease that may not be apparent to the surgeon intra-operatively. The association between LDD and CS is of particular interest. The coexistence of these two rare disorders has previously been under-recognized and under-reported. The detection of a case with LDD should prompt the neurosurgeon to collaborate with internal medicine to look for CS, which has a more dramatic prognosis. Conversely, patients with CS should routinely be screened for a posterior fossa lesion (LDD) by the treating physician. Recognition of this association has direct clinical relevance; diligent long-term follow-up monitoring of patients with LDD and CS may lead to early diagnoses of cancers.

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