Acta Neurochir (Wien) (2004) 146: 679–690
DOI 10.1007/s00701-004-0264-x

Acta Neurochirurgica
Printed in Austria

Clinical Article

Lhermitte-Duclos disease and Cowden disease: clinical and genetic study in five patients with Lhermitte-Duclos disease and literature review

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Published online May 21, 2004

Summary

Background. Lhermitte-Duclos Disease (LDD) is an infrequent cerebellar disorder characterized by focal or diffuse enlargement of cerebellar folia presenting as a slowly growing mass in the posterior fossa. Over the past decade its association with Cowden disease (CD) has been recognized with increasing frequency. This latter disease is a genetic condition leading to the presence of multiple hamartomas and neoplasias which affect mainly the skin, thyroid, breast and genito-urinary and gastro-intestinal tracts. It has even been hypothesized that LDD and CD constitute a single entity. This work is aimed to analyse to what extent this association was present in patients treated for LDD at our institution.

Method. We reviewed the medical records of five patients and performed clinical studies for CD manifestations, among them, genetic investigation for PTEN mutations. The International Cowden Consortium Criteria were applied for the diagnosis of CD.

Findings. Four of the five patients treated for LDD were also diagnosed of CD. The genetic study found PTEN mutations in two of them.

Interpretation. LDD has been found to be closely related to CD in this series, in accordance with previous literature. However, the absence of CD diagnosis in one of the patients led us to suggest that, despite the strong association between these two diseases, LDD can also appear as an isolated condition.

Keywords: Lhermitte-Duclos disease; Cowden disease; PTEN gene; cerebellum; gangliocytoma; dysplasia.

Introduction

Lhermitte-Duclos Disease (LDD), or Dysplastic Gangliocytoma of the cerebellum, is a slowly growing benign lesion the nature of which (hamartoma, neoplasia or congenital malformation) has still not been precisely defined. It consists of a focal or diffuse engorgement of cerebellar folia behaving as a space-occupying lesion [43, 44, 56].

Though benign in nature, the lesion in LDD shows progressive growth and surgical excision appears to be the only effective treatment to definitely relieve the symptoms [16, 37].

There are approximately a hundred and fifty reported cases of LDD. Many other concomitant diseases have been frequently described in these patients such as neurological disorders, cutaneous lesions, dysmorphic features and tumors [23, 40, 54]. In some cases these lesions were seen in the context of Cowden Disease (CD) [15, 40, 44], which is a genetic condition characterized by the presence of cutaneous and non-cutaneous hamartomas as well as breast, thyroid, gastro-intestinal and genito-urinary neoplasias [15, 35, 40]. This disorder is caused by the mutation in PTEN gene at chromosome 10q22-23 [26, 35].

The co-existence of LDD and CD in the same patient has been recognized with increasing frequency over the past decade, leading many authors to consider that LDD is a neurological manifestation of CD [40, 44]. It has also been suggested that CD is very frequently overlooked in patients treated for LDD [44]. However, it is

not yet clear whether this cerebellar lesion appears only in the context of the more complex CD syndrome, or may appear alone. In any case the diagnosis of CD is of great importance to allow screening and early detection of cancers derived from this condition.

The objective of this study was to assess the association of LDD and CD in patients treated for LDD at our hospital. For this purpose data regarding LDD presentation, the presence of CD manifestations, and the sequence of PTEN gene were studied and compared with cases reported in the literature.

Patients and methods

A total of five cases of LDD were found in the Neuropathology Service's registry (1976–2002). Medical records were reviewed for clinical, radiological and histopathological data concerning LDD and special attention was paid to the presence of symptoms or signs suggesting CD.

Thus a thorough history, clinical examination, and thyroid and genito-urinary ultrasonography were performed in the four living patients in April 2002. The International Cowden Consortium (ICC) diagnostic criteria were used for clinical diagnosis of CD (Table 1) [15, 35]. Macrocephaly was diagnosed when the occipitofrontal head circumference was greater than 98th centile ($>$58 cm in women and $>$58.5 cm in men) [40].

The following step in this investigation was the genetic study for PTEN mutations by the "Program of Genetic Counselling in Familial Cancer" of CNIO ("Centro Nacional de Investigaciones Oncológicas", Instituto Carlos III). Blood samples were taken from the patients to analyse leucocyte DNA. The nine exons of PTEN gene were amplified by PCR and studied by direct sequentiation.

Pub-Med was searched for previous cases of LDD, especially those associated with CD. LDD was the only key word used. Related articles were also consulted when necessary. Data extracted from the literature were compared with those regarding our patients.

Results

Of the five patients with the diagnosis of LDD two were women and three men, of ages ranging from eleven to fifty-six years. Clinical data are summarized in Table 2.

By examining the clinical records it was realized that only one patient had been considered to be probably affected by CD (Case no 4), despite that the available data were sufficient to definitely diagnose this disease. The medical history of another patient (Case no 3) also allowed to establish the diagnosis of CD based on the association of macrocephaly and mental impairment with LDD. Concomittant conditions raised the suspicion of CD in one more patient (Case no 5). Finally, the remaining two patients had not shown any associated signs or symptoms suggesting CD.

The studies performed in search for CD reinforced this diagnosis in patient no 4 and provided data to also make the diagnosis in patients no 1 and no 5. Patient no 2 did not match the criteria for diagnosis of CD. Unfortunately patient no 3 could not have additional investigations as he died before the present study was

Table 1. *International Cowden Consortium criteria for the diagnosis of Cowden disease (CD) [15]*

CD manifestations		Operational diagnosis
Pathognomonic criteria:	facial trichilemmomas	*in a person:*
Mucocutaneous lesions	acral keratoses papillomatous papules mucosal lesions	1. mucocutaneous lesions alone if: – 6 or more facial papules, of which 3 or more must be trichilemmomas; or – cutaneous facial papules and oral mucosal papillomatosis; or – oral mucosal papillomatosis and acral keratosis; or – palmoplantar keratosis, 6 or more.
Major criteria	breast carcinoma thyroid carcinoma (non medullary) macrocephaly ($\geq$95th centile) Lhermitte-Duclos disease endometrial carcinoma	2. 2 major criteria but one must include macrocephaly or Lhermitte-Duclos disease. 3. 1 major and 3 minor criteria. 4. 4 minor criteria
Minor criteria	other thyroid lesions mental retardation (IQ $\leq$ 75) gastro-intestinal hamartomas fibrocystic disease of the breast lipomas fibromas genito-urinary tumors or malformations	*in a family were a person is diagnosed with CD*: 1. the pathognomonic criterion/a 2. any one major criterion with or without minor criteria. 3. 2 minor criteria.

Table 2. *Data regarding clinical presentation of Lhermitte-Duclos disease and diagnosis of Cowden disease (CD) prior to this study*

Case no and date of operation	Age (yrs) & sex	Symptoms and signs at presentation	MRI	Recurrency (date)	Diagnosis of CD before this study
1 (1989)	27 M	– headache – cerebellar tremor	typical	yes (1994)	no
2 (1990)	56 M	– headache – unstable gait – dizziness	not done	no	no
3 (1994)	12 M	– ataxia, dysmetria dysartria. – headache – visual loss	typical	residual lesion (1997)	no
4 (1997)	26 F	– seizures	typical	no	probable
5 (1997)	21 F	– headache – vertigo	typical	no	no

Table 3. *Cowden disease (CD) manifestations in our five patients. Data obtained after reviewing clinical records are marked as x, while newly diagnosed manifestations are marked as* **X**

CD Manifestations		Patient				
		1	2	3	4	5
Pathognomonic criteria:	facial trichilemmomas					
	acral keratoses		**X**		x	**X**
Mucocutaneous lesions	papillomatous papules					
	mucosal Lesions				**X**	**X**
Major criteria	breast carcinoma					
	thyroid carcinoma (non medullary)				x	
	macrocephaly	**X**		x		**X**
	Lhermitte-Duclos disease	x	x	x	x	x
	endometrial carcinoma					
Minor criteria	other thyroid lesions	**X**				**X**
	mental retardation			x		
	GI hamartomas				x	
	fibrocystic disease of the breast					
	lipomas				x	**X**
	fibromas		**X**		x	
	genitourinary tumors or malformations				x	**X**
	PTEN mutations				**X**	**X**

GI Gastrointestinal.

undertaken. In summary four patients in this series met the diagnostic criteria for CD (Table 3).

Case reports

Case 1

A 26 year-old man presented in may 1989 with headache and progressive tremor affecting his head and left arm. Cranial CT scan showed a medial hypodense cerebellar mass without contrast enhancement that compressed the fourth ventricle and the basal cisterns, producing secondary triventricular hydrocephalus. On MRI the lesion, which involved the vermis and medial left hemisphere, appeared hyperintense in T2 sequences and iso-hypo-intense in proton density sequences with a laminated pattern in coronal images. A second incidental rounded lesion 1–1.5 cm in diameter, iso-intense in proton density and slightly hyperintense in T2 images, was seen at the right frontal lobe, suggesting cortical heterotopia. Angiography demonstrated the presence of engorged draining veins in relation with the cerebellar lesion.

The patient underwent ventriculoperitoneal shunting and subsequent tumor resection through a suboccipital craniectomy and C1 laminectomy. Cerebellar folia appeared widened and flattened, whitish in colour and softer than normal tissue in consistence. The lesion was quite vascularized. The histopathological study showed the typical findings of LDD.

Five years later a CT demonstrated recurrence of the lesion and the patient was re-operated on at another centre with the same pathological findings.

We examined the patient in search of CD manifestations when he was 39 years old. Follow up neuroradiological studies at another

centre had shown a small remnant of the cerebellar lesion stable in size. Physical examination failed to demonstrate mucocutaneous lesions. His head circumference was 60.7 cm. Ultrasonographic study of the thyroid gland showed undiagnosed multinodular goitre. CD diagnosis was made on the basis of the association of macrocephaly and LDD and thyroid disease supported this diagnosis. In addition he reported the presence of mental impairment in four paternal cousins and a paternal niece had died as a result of an intracranial astrocytic neoplasm. Antecedents of other CD related alterations were absent.

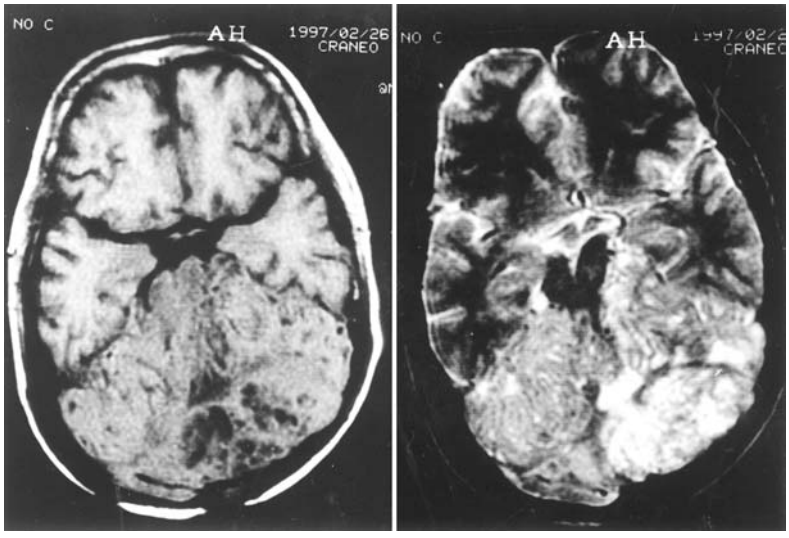

Fig. 1. Case no 3: MRI study shows the typical picture of Lhermitte-Duclos disease. Both cerebellar hemispheres are entirely involved. Left: T1 sequence, right: T2 sequence. Severe enlargement and distortion of posterior fossa with obliteration of the fourth ventricle and compression of the brain stem can be appreciated

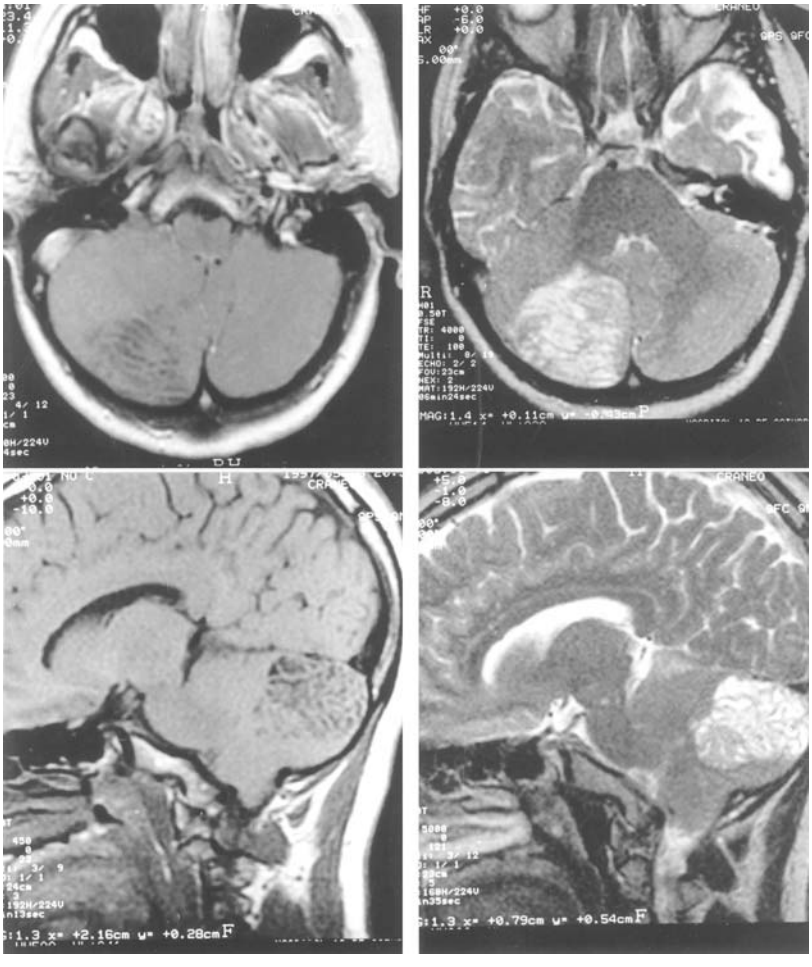

Fig. 2. Case no 4. MRI study shows the classic finding of a focal, nonenhancing cerebellar mass in the right hemisphere, hypo-intense on T1 weighted images (left) and hyperintense on T2 (right), along with the curvilinear stripes that are iso-intense to the cerebellar cortex on both sequences. The lesion caused slight or nil mass effect over the fourth ventricle and there was no hydrocephalus

Case 2

In May 1990 a 56 year-old man was admitted with a 5-month history of dizziness, unstable gait, episodes of diplopia and progressive occipital headache with vomiting developing during the month prior to consultation. Cranial CT scan demonstrated an isodense left cerebellar mass with mild contrast enhancement, which compressed the fourth ventricle and caused secondary hydrocephalus. MRI was not performed.

The patient underwent ventriculoperitoneal shunting and tumour excision through a posterior fossa craniectomy. Left cerebellar hemisphere and tonsil appeared enlarged and whitish during the operation, with thickened convolutions. LDD was suspected based on this appearance. Histopathological study confirmed this suspicion. Control CT and MRI studies did not show recurrence of the lesion.

We readmitted the patient to check the presence of CD at the age of 68. Familial and personal history was irrelevant (he had two healthy daughters). On physical examination he presented small papules around the neck and in both axillae, and multiple small keratotic lesions around the ankles, which were diagnosed by the dermatologist as fibromas and keratosis, respectively. The rest of the examination was normal. Ultrasonograpy showed no anomalies of the thyroid gland and a simple renal cyst was found on nephro-urological study. Despite LDD and cutaneous keratotic lesions the patient was not diagnosed with CD according to the ICC criteria.

Case 3

This child was studied since birth because of macrocephaly and later on because of delayed psychomotor development with manipulative clumsiness and dysmetria. Cerebral ultrasonography during the neonatal period showed a normal ventricular diameter, and a cranial CT performed at the age of two was considered normal. He was diagnosed at the age of seven to suffer hydrocephalus after clinical worsening and development of gait ataxia, but his parents refused further investigations or treatment. However, at the age of ten they consulted again because of progressive headache, deterioration of cerebellar symptoms and signs and visual loss. CT scan showed important obstructive hydrocephalus secondary to obliteration of the fourth ventricle, with an abnormally enlarged cerebellum bulging and thinning the occipital bone, alteration interpreted as a malformation. A ventriculoperitoneal shunt was placed. However, progressive distortion of the fourth ventricle along with the presence of bilateral hypodense areas in the cerebellum observed on subsequent studies led to the suspicion of LDD. Partial resection of the lesion was performed at the age of 12 years, confirming this diagnosis. Follow-up neuroradiological studies detected the growth of the remaining lesion, with wide striated areas affecting both cerebellar hemispheres on MRI (Fig. 1) and clinically the patient developed lower cranial nerve dysfunctions. A second operation was carried out at the age of fifteen. Few months after surgery the patient died as a consequence of aspiration pneumonia.

His brother was also macrocephalic without other known lesions. His mother died at the age of 45 with disseminated breast cancer.

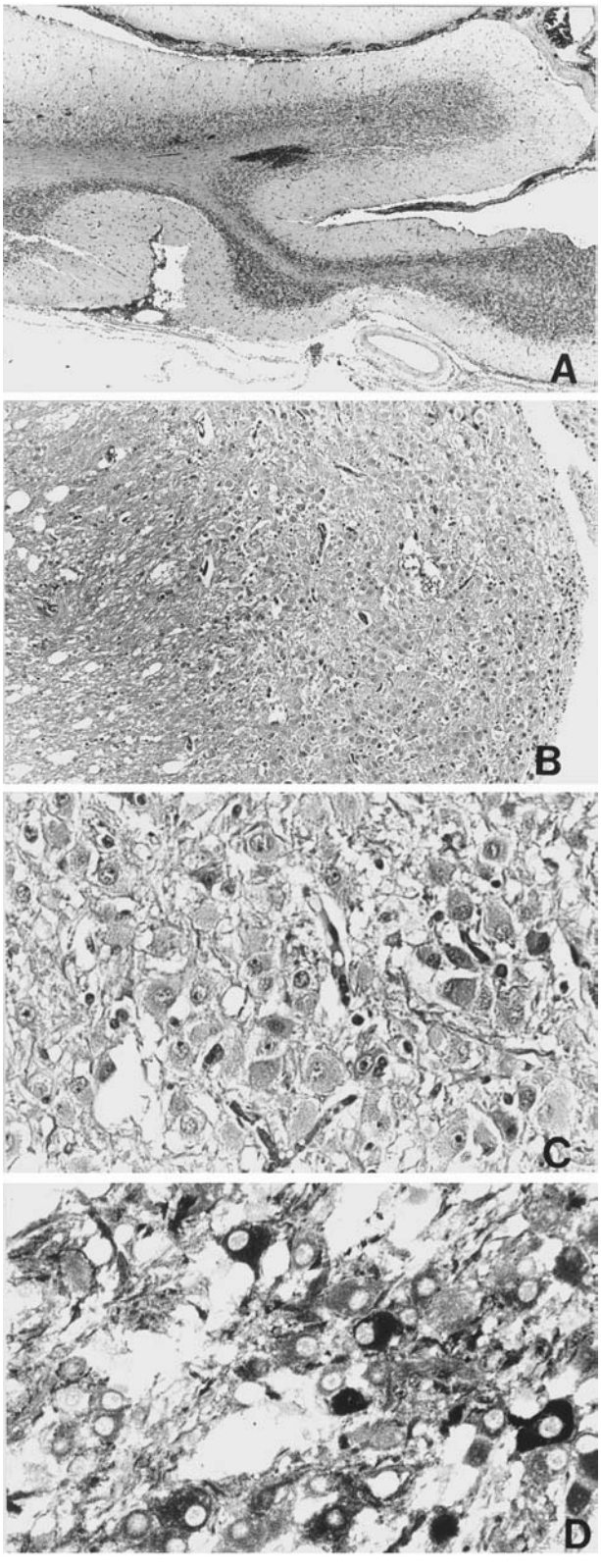

Fig. 3. Case 5: (A) Low power microphotograph showing a cerebellar folia partially affected by Lhermitte-Duclos disease. The normal three-layered pattern can be observed in the greater part of the image, but in the left superior corner the granules progressively disappear, being substituted by a thicker band of ganglionic-like neurons. At this point the enlargement of the molecular layer is also seen. H & E ×100. (B) The abnormal, ganglionic neurons and enlarged molecular layer are shown, with absence of the atrophic white matter axis. H & E ×200. (C) Abnormal neurons showing abundant eosinophilic cytoplasm, big nucleus with dispersed chromatin and occasional nucleolus, but no mitosis or atypia can be seen. H & E ×400. (D) The abundant cytoplasm stains intensely with neuronal markers. Neuron specific enolase ×400

Although we could not directly study the patient we established the diagnosis of CD based on the association of LDD and macrocephaly.

Case 4

A 27 year-old woman was diagnosed with a left cerebellar mass after suffering two generalized tonic-clonic seizures. The hypodensity of the lesion on the CT and the typical MRI appearance led to the preoperative diagnosis of LDD (Fig. 2). Frontal foci of gliosis, and the sequelae of a cerebral contusion secondary to a head trauma involving the right temporal lobe were also noted. She had previously been diagnosed with adenomatous polyposis coli (APC) with carcinomatous degeneration undergoing total colectomy. She had also been treated for follicular thyroid carcinoma with subtotal thyroidectomy and I^{131} and operated on because of subcutaneous lipomas. An investigation for other CD manifestations showed ovarian cysts, palmoplantar keratosis and facial fibromas. The patient was considered probably affected with CD and was submitted to our centre for treatment of LDD. Total excision of the lesion was performed and the diagnosis of LDD was confirmed pathologically.

We saw the patient at the age of 32. She presented oral papillomatosis and abnormal teeth alignment in addition. She had also been diagnosed with gastric polyps. Her father had died as a result of colonic carcinoma secondary to APC. Her sister had undergone total colectomy because she was also affected, and was later operated on because of a serous ovarian cysto-adenoma and benign breast nodules in the context of fibrocystic breast disease.

Case 5

A 21 year-old woman was diagnosed with a cerebellar lesion causing obstructive hydrocephalus after an 18-month history of headache and vertigo. MRI suggested LDD, with a typical striated image. This diagnosis was confirmed after total resection and histopathological study of the lesion (Fig. 3). Preoperative study showed pectus excavatum and diffuse normofunctioning goitre.

When we studied the patient in search for CD manifestations physical examination demonstrated macrocephaly (occipitofrontal head circumference = 63 cm), multiple facial papules, oral papillomatosis, palmoplantar keratosis (Fig. 4) and subcutaneous lesions suggesting lipomas. She had been operated on in 2001 for a large right ovarian cyst after consulting for acute abdominal pain. Pathological study only showed hemorrhagic necrosis, attributable to ovarian torsion. Familial antecedents of common cancerous diseases were numerous but failed to show a clear pattern of inheritance.

We did the diagnosis CD based on the association of multiple cutaneous and non-cutaneous criteria.

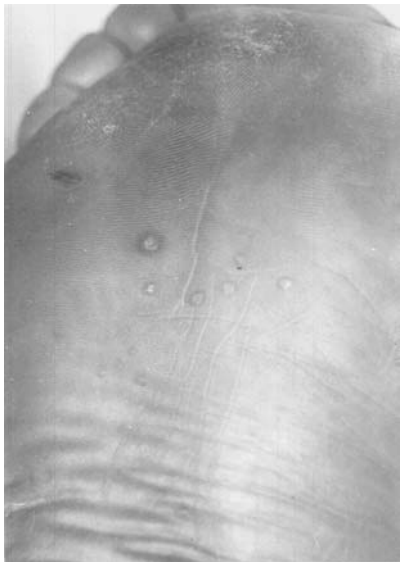

Fig. 4. Case no 5. A plantar cluster of small keratotic lesions is shown

Genetic study

Genetic study was performed in the four living patients. The analysis of PTEN revealed a normal sequence in patients 1 and 2.

Patient 4 presented a mutation in PTEN consistent in the substitution of a guanine by an adenine in exon 6. The study of PTEN in patient 5 showed the presence in exon 1 of a deletion in two consecutive bases of adenine leading to a stop codon.

Despite the association of CD with gastro-intestinal hamartomas, the presence of multiple colonic polyposis in patient 4 prompted the study for mutations of the APC gene that locates at 5q21-q22. A mutation was found at codon 541 in exon 12 consisting in the insertion of a guanine. This mutation results in the synthesis of a truncated protein.

Information was given to the Primary Attention Physicians of the patients and those specialists attending the newly diagnosed lesions.

Discussion

The pathological substrate of thickening of the cerebellar folia occurring in LDD is the substitution of the normal three-layered cerebellar cortex by an enlarged molecular layer over a gross band of ganglionic-like cells, the latter occupying the place of Purkinje and granular cell layers [56]. The enlarged molecular layer is composed of hypertrophic hypermyelinated and non-myelinated axons originating from underlying abnormal cells [59]. These abnormal cells have been demonstrated immunohistochemically to be of neural origin and appear to be divided into two types [18, 56]. The major part of abnormal neurons present immunohistochemical and ultrastructural features of granule cells, and many authors have considered that they represent hypertrophic granules, sending their axons into the molecular layer [16, 59]. The other population of cells, representing less than 10%, resembles immunohistochemically Purkinje cells [18, 47]. No mitosis, atypia or pleomorphism have been described in these cell populations [56], and there are no normal cells included between them [18], suggesting that the lesion does not have an invasive behaviour. The lesion margins are characterized by the progressive increase of the diameter of convolutions and the disappearance of normal granules and Purkinje cells that are substituted by the abnormal ones. Normal and abnormal cells co-exist at the borders of the lesion, with a gradual transition from normal cerebellum into

the pathological tissue. The axis of white matter appears spongiotic and atrophic. The presence of small vessels in the leptomeninges and subpial molecular layer whose walls can appear calcified, has been reported [23, 32, 40]. Tumoral progression of LDD into more aggressive neoplastic lesions has not been described [56].

The exact nature of this lesion remains unclear. Neoplastic, dysplastic and hamartomatous origins have been proposed [37, 44]. Most authors tend to consider that LDD is an hamartomatous lesion [21, 40, 44]. However, in spite of the immunohistochemical resemblance of the cells that compose the lesion with Purkinje and granular cells, they are different from these or any other mature cell in the CNS. This fact precludes the classification of this lesion as a hamartoma [11, 43].

The absence of atypia, mitosis, proliferation or invasion excludes the neoplastic nature of LDD [18, 28, 43]. The growth of LDD seems to be due to cell hypertrophy and the recurrences may be explained by the difficulties in removing the lesion borders, which appear ill defined [18].

The term dysplasia has been frequently used in LDD, also termed ''Dysplastic gangliocytoma of the cerebellum''. Dysplastic tissue is considered the most disorganised of non-neoplastic proliferation patterns, sometimes preceding neoplasia [11], sharing with LDD the alteration in the normal appearance of the tissue due to changes in the normal shape and size of cells. However, the absence of proliferation prevents the consideration of LDD as a dysplastic lesion.

Functional studies have tried to disclose whether this lesion behaves metabolically as neoplasia or as normal tissue, and the results are as controversial as pathological studies since LDD shows some features suggesting neoplasia and others similar to those found in normal tissue [20, 38, 39, 41].

In conclusion, morphological, ultrastructural and immunohistochemical studies indicate that LDD is composed of cells different from those indigenous of the cerebellum, but sharing some features with them [43, 56]. They appear hypertrophic and an increase on protein metabolism has been demonstrated [59]. The progressive growth of the lesion in absence of cellular proliferation, the gradual transition with normal cerebellum and the recurrences described when it is not totally removed suggest that this lesion extends through the progressive transformation with hypertrophy of the normal cerebellum at the margins with the lesion [18]. The mechanism by which this process develops has still not been completely understood and is commented on below. Animal studies are being currently performed which may shed some light on this issue [5, 24].

Clinical findings of LDD

LDD is a relatively rare disease. It has been reported in all age groups (from birth to 74 years of age) with a mean age at presentation of 33.7 years. There is no sex predominance [29, 54].

Patients may be asymptomatic for years or present long symptomatic periods before diagnosis (until 29 years) [16, 42] with a mean duration of symptoms of 46 months. Sometimes LDD is found incidentally in imaging or necropsic studies [23, 29, 54].

Clinical manifestations are related to a posterior fossa mass effect and secondary obstructive hydrocephalus. An intracranial hypertension syndrome with headache (70%) and ataxia is the most frequent complaint at presentation [16, 21, 29, 37, 44, 54]. Cerebellar signs or symptoms are present in approximately 40–50% of the patients [29, 40]. Cranial nerve palsies (30%), long tract dysfunction (30%), visual disturbances, neck stiffness, tinnitus, dizziness, orthostatic hypotension, vertigo, psychiatric symptoms, acute deterioration due to decompensated hydrocephalus and subarachnoid haemorrhage are less frequent manifestations [16, 21, 29, 37, 42]. Some patients have been diagnosed after presenting with seizures attributed to an other anomaly [40] as occurred in our patient no 4, in whom we could not discern whether seizures were caused by the temporal scar caused by a previous brain contusion, or by the frontal foci of gliosis.

Overall, clinical presentation in our patients does not differ much from the previously reported cases. The clinical course in patient no 3 has special interest because of the long lasting and slowly progressive clinical evolution. This case was previously reported by Verdu *et al.* [53] and taking into account the clinical and neuroradiological signs they argued that LDD was already present in early infancy or even at birth in this child, although this latter suggestion could not be confirmed. In any case, the characteristic slow growth of LDD is typically illustrated by this patient, who suffered a progressive distortion of the fourth ventricle and enlargement of the posterior fossa during more than a decade.

Diagnosis

The definite diagnosis of LDD is histopathological. However, since the introduction of MRI, which clearly shows the typical striated, laminated or ''tiger striped''

appearance of the involved cerebellar tissue, diagnosis can be achieved preoperatively [9, 16, 23, 27, 43, 48]. This imaging picture is produced by the close apposition of thickened cerebellar folia, which have lost secondary arborisation, explaining the alternation of different tissue intensities. The atrophic white matter, the adjacent layers of abnormal ganglionic neurons and the most inner part of molecular layers are seen with prolonged signal (hypo-intense on T1 and hyperintense on T2). The outer part of the molecular layer of adjacent folia and the almost virtual leptomeningeal space lying between them are seen as iso-intense with normal cerebellar tissue both in T1 and T2 sequences [23]. LDD is the only tumoral lesion that respects the cerebellar convolutions despite its enlargement, and this feature allows a preoperative, almost certain, diagnosis [23, 27, 43]. Only cerebellar infarction produces a similar distortion, but the clinical presentation is sufficiently distinctive [27]. However one should remember that the typical striated pattern may not be present in infants [23, 27].

MRI is the most sensitive test to show the laminated pattern and is more precise for defining the limits of the lesion in order to accomplish the most radical excision during surgery. It is also superior for showing the presence of small portions of either remaining or recurrent lesion during follow up, MRI should be used for diagnosis, treatment planning and follow up in this disease [16, 23, 27, 31, 42].

On the CT scan the lesion of LDD is seen as hypodense or iso-hypodense [29, 42] showing sometimes the alternating iso-hypodense image on high resolution studies [23, 31]. Calcifications may be present [23, 27, 29, 31, 42] and sometimes angiography or MRI can show enlarged draining veins [57, 58] as occurred in patient no 1.

Treatment of LDD

Despite its benign nature the progressive growth of the lesion demands surgical excision [16, 43, 44]. Some authors favour conservative management, mainly in cases of incidental findings, arguing that derivative/decompressive procedures can achieve an improvement of symptoms [23, 41, 51, 52]. However there are data mitigating this conservative approach. Follow up is short in cases treated conservatively and it is well known that LDD progresses slowly. In addition, some patients initially managed without surgery have eventually needed surgical excision [44] as occurred in our patient no 3. The adverse outcomes observed in patients with LDD before the availability of modern imaging studies, particularly MRI, allowing a more appropriate planning of surgery [37, 42, 44] also favour a radical therapeutic approach.

Though total excision is difficulted due to the progressive transition and ill-defined margins between normal and pathological tissues [43, 44, 52] it should be attempted because recurrences appear to be more common when subtotal resection is performed [42, 54, 57].

Radiation therapy has been reported as non effective in avoiding the growth of the lesion [44] and the absence of cellular proliferation in pathological studies makes its usefulness [37] doubtful.

It has recently been suggested that metabolic testing may allow one to distinguish cases of LDD that will progress from those that will not, helping to select patients for conservative management [37, 41], but more data are needed to clarify whether these tests can predict the potential for growth of the lesion.

Lhermitte-Duclos disease and Cowden disease

LDD patients are usually affected by many other clinical problems [40]. These frequently involve the CNS as megalencephaly (in approximately 50% of cases), mental impairment, epilepsy, hypo-acusia, heterotopias, microgiria, syringomyelia, hypertrophy of olivary nuclei, choroidal hamartoma, gliosis, low and high-grade gliomas, and meningiomas [14, 16, 25, 40, 42–44, 54, 55, 57]. The skin and soft tissues are also usually involved with lesions such as trichilemmomas, angiomas, cavernous haemangiomas, cafe au lait spots, lipomas, angiolipomas, fibromas, conjunctival papillomas and cystic hygroma [10, 12, 44, 54, 55]. Dysmorphic anomalies such as large hands or feet, large thumb, polydactilia and high arched palate have also been described [54]. Benign and malignant neoplasms involving thyroid, breast, gastro-intestinal and genito-urinary tracts, liver, parotid gland, lung and skin have been reported in patients with LDD [54].

It was not until 1991 when the association of several of these conditions in two patients with LDD were recognised to be in relation with CD [40]. This latter disease is a genetic condition characterized by the presence of multiple hamartomas and neoplasms affecting the skin and many other organs, mainly the thyroid gland, the breast, and genito-urinary and gastro-intestinal tracts [15, 35, 49]. Its prevalence has been estimated to be 1 in 200.000 people, although this may be an

underestimation [15]. Skin lesions, those characterizing this syndrome, are present in more than 90% of the patients [15, 35] and consist mainly of trichilemmomas, but also mucosal papillomatosis, fibromas and akral keratosis. Cutaneous lesions common to other phakomatosis, such as cafe au lait spots, may also appear in CD. Approximately two thirds of patients are affected by thyroid disorders which [21, 49, 55] consist of benign lesions in most of them; however follicular or papillary carcinomas can also occur in 10% of the cases [26]. The breast is affected in nearly 75% of women with CD [21, 49] in the form of benign lesions or carcinoma. Thirty to fifty per cent of women affected by CD suffer breast carcinoma [26, 44, 49, 55], at an average age of 38 [55] and the disease is bilateral in one third of cases [44]. Other manifestations of this syndrome include dysmorphic features, macrocephaly (up to 80%) and neurological disorders such as meningiomas, dural arteriovenous malformations, hearing loss, diffuse cerebellar hypertrophy, mental impairment and seizure disorders [40, 45, 49]. This disease may appear sporadically or with an autosomal dominant inherited pattern. Penetrance appears to be age related and expressivity is highly variable [15, 44, 49], with cases displaying many features of the disease and others showing only subtle cutaneous manifestations.

The aetiology of this genetic disorder has been recently related to be the mutation of the PTEN gene localized in 10q22-23 [26, 34, 35] (alteration also found in Bannayan-Riley-Ruvalcaba syndrome, an allelic condition) [15, 44] PTEN gene encodes a phosphatase/tensin homologue protein that has been implied in tumour suppression (its mutation promotes proliferation and invasion and inhibits apoptosis) and embryonic development of germ cells into endo-, meso- and ectodermal layers [26, 44]. Recent molecular studies with mice embryos demonstrate that homozygous mutations are not compatible with life, producing the inability of cells to develop and form into the three germinal layers [13]. Heterozygous mutations have a tendency to develop dysplastic-hyperplastic lesions and neoplasms in the skin, gonads, prostate, thyroid and colon. Selective inactivation of PTEN in neuronal populations in mice causes macrocephaly, ataxia and seizures, with augmented neuronal soma size and absence of abnormal cell proliferation in pathological studies [5, 24]. These findings reflect very well the implication of PTEN in the development of ectodermic, mesodermic and endodermic tissues, all of which may be affected in CD on one hand, and the role of its mutations in the neurological alterations found in CD [15] and LDD patients on the other. When PTEN has been studied in pathological specimens of CD hamartomas the two alleles have been found mutated [44] and the mutated allele has been shown to be expressed in the cerebellar lesion of 83% of patients with LDD [19, 60].

The coincidence of these two rare diseases in two patients, the similarities of their associated conditions, and the description of familial cases of LDD led Padberg *et al.* [40] to postulate that they could be related to each other. The presence of associated neurological disorders in CD patients, the involvement of skin and endoderm derived structures, and the tendency to develop malignancies made them to consider CD as a new phakomatosis in which LDD represented one CNS manifestation among others such as megalencephaly, mental impairment, seizures, gliosis or heterotopias. Since the description of the initial two cases, 34 more patients with concomitant LDD and CD have been described [1–3, 6, 8, 10, 19, 21, 22, 27, 30, 31, 33, 34, 40, 41, 43, 44, 50, 52, 54, 55, 57]. Most are case reports, but there are also two series [44, 52] in which cases were retrospectively studied in search of the diagnosis of CD. In one of these series five patients with LDD where also diagnosed with CD [44]. In the other series [52], there was a patient who met the diagnostic criteria to be definitely diagnosed, four more patients exhibited a high degree of suspicion, and one did not present any other criterion; this last patient however was only 5 years old and the age related penetrance of CD lesions prevented the exclusion of the diagnosis.

The above mentioned evidence has led some authors to argue that LDD with its associated conditions represents the same entity as CD [44]. However others doubt whether this is entirely true or LDD may appear as an isolated condition [18, 31]. In fact, after the article of Padberg *et al.* [40] 55 cases of LDD without the diagnosis of CD have been reported in the literature. Unfortunately, in the great majority there is no information as to whether the existence of CD was investigated, but there are cases in whom the study failed to demonstrate associated conditions [18].

In our series four out of the five patients were clinically diagnosed as suffering from CD, supporting the strong association of CD and LDD. In patient no 3, who could not undergo additional studies, diagnosis was established on the basis of the following data: the presence of LDD, macrocephaly, mental impairment and familial antecedents of macrocephaly in his brother and breast cancer in his mother, which are consistent criteria for a retrospective diagnosis of CD. Patient no 2 was the

only one that did not met the ICC criteria despite the presence of keratotic lesions and a renal cyst. These two lesions, also present in patients without CD, were interpreted as coincidental, and not related to this syndrome. However, it is not possible to rule out a paucisymptomatic presentation of CD in this case. Patient no 1 did not show cutaneous lesions, but the presence of LDD allows the diagnosis of CD even in the absence of this manifestation if there is one other major feature, such as macrocephaly, as occurred in this patient [44]. Patient no 4 suffered both CD and APC. The concurrence of these two autosomal dominant diseases is in our opinion exceptional and fortuitous.

Genetic alterations are found in approximately 80% of patients with the clinical diagnosis of CD [15]. Genetic study to detect germline PTEN mutations in LDD has been performed in a minority of CD patients, and up to date this genetic alteration has been found in 17 patients with LDD to our knowledge [19, 21, 22, 36, 44, 31, 41, 50, 60]. We found genetic mutations in two of the four LDD patients studied (two of the three alive with CD). One of the patients with the diagnosis of CD (patient no 1) and the patient who was unaffected by this syndrome did not show PTEN mutations, but it should be noted that the absence of genetic alterations on the PTEN gene does not exclude CD [36]. These alterations may lie on introns or sequences distant to the gene but implied on the regulation of transcription or splicing, or may consist on deletions of entire exons [33, 36].

LDD could be considered as a typical lesion of CD which can also manifest out of the context of this syndrome, as schwannomas do in Neurofibromatosis type 2 (NF2) and haemangioblastomas in von Hippel-Lindau disease (VHL). Genetic diagnosis is confirmed in approximately two thirds of the patients with NF2 [46] and in 80% of patients with VHL [17], a proportion very similar to that found for CD in our and other series [15, 36]. In contradiction to this analogy is the frequency with which the tumoral conditions appear isolated or in patients with more complex diseases. Only 3–4% of patients with neurinomas are affected with NF2 or Schwannomatosis [4, 46], and only 25% of patients with haemangioblastomas suffer VHL [7]. However, LDD presents in most cases associated with other ''pathologies'' in the context of CD, but more rarely in an isolated form.

Finally, the low frequency with which CD has been looked for in LDD patients should be emphasized. The present and previous studies [44] have shown that CD is probably underdiagnosed in patients with LDD, thus precluding an appropriate management.

Conclusions

LDD is a rare cerebellar disorder, which usually appears in the context of a more complex syndrome, i.e., CD. However, despite the association of these two diseases in our and other series, the literature indicates that LDD can also manifest itself in an isolated form. The high frequency with which LDD presents in the context of CD makes it mandatory to rule out this later disorder in all cases of LDD in order to allow early detection and treatment of associated neoplasms. Only a systematic search for associated CD in all patients with LDD either prospectively or retrospectively will clarify the true relationship between these two rare diseases.

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Comments

In this very thoughtful report from Madrid, Perez-Nunez and co-authors report an association between Lhermitte-Duclos Disease or dysplastic cerebellar gangliocytoma (LDD), and Cowden Disease, the multiple hamartoma-neoplasia syndrome (CD). They reviewed the medical of patients treated at their institution over three decades for LDD and identified five patients, four of whom also had CD. This study corroborates the strong association between LDD and CD. The absence of a diagnosis of CD in one patient (case 2) led the authors to suggest that LDD can also appear as an isolated entity. Other institutions, including our own (authors' reference 52) have identified an association between LDD and CD. In the five patients diagnosed with LDD at our institution over the past 40 years, all also exhibited manifestations of CD. We believe that CD is a true phakomatosis, with hamartomas involving the cutaneous and neural ectoderm. The finding of Perez-Nunez and others that LDD can occur as an isolated entity does not disprove the hypothesis that CD is a true phacomatosis. I suspect that CD presents as a spectrum which sometimes includes LDD and sometimes does not. It is interesting that the one patient in the present series who had LDD but not CD did have cutaneous keratotic lesions and a renal cyst. My recommendation is that this patient be monitored closely for manifestations of CD.

I congratulate the authors on an excellent and thoughtful analysis. This manuscript series does remind us that LDD and CD are two rare disorders whose coexistence has previously been under-recognized and under-reported. The presence of one of these disorders should prompt the clinician to search carefully for the presence of the other.

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Pérez-Núñez *et al.* report on 5 personal cases of Lhermitte-Duclos disease (LDD) after having search for the classical association with Cowden disease (CD) in these cases.

The clinical material is thoroughly analysed concerning all the clinical aspects of both diseases and as an ''icing on the cake'' the modern molecular description of the PTEN mutation, known to be found in most of the CD patients and also in some of the LDD patients, is presented. Relapse of the disease in case of partial removal confirmed other reports of the literature. The authors should be thanked to have provided a complete review on this rare subject to the neurosurgical community, emphasizing the importance of the genetic screening of these patients, especially when considering genetic counselling.

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