Cowden disease and Lhermitte–Duclos disease: an update

Case report and review of the literature

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Object. Cowden disease is a rare autosomal-dominant phacomatosis and cancer syndrome that is associated with Lhermitte–Duclos disease (LDD), also called dysplastic cerebellar gangliocytoma.

Methods. In this review the authors summarize the additions to the literature during the past 5 years, with emphasis on new case reports and advances in imaging and molecular biology. Adult-onset LDD is now considered pathognomonic for Cowden disease.

Approximately 220 cases of LDD have been reported. Magnetic resonance imaging in patients with LDD is often diagnostic, and imaging studies have facilitated accurate diagnosis and contributed to the improved outcome in affected patients. Cowden disease and other rare, related disorders, such as Bannayan-Riley-Ruvalcaba, Proteus, and Proteus-like syndromes, are often caused by mutations of the PTEN gene.

Conclusions. Because of the high incidence of systemic cancer in patients with Cowden disease, it is important for neurosurgeons to recognize the association between this disease and LDD and to refer affected patients for appropriate cancer screenings and interventions.

KEY WORDS • Cowden disease • dysplastic gangliocytoma • hamartoma • Lhermitte–Duclos disease • phacomatosis • PTEN gene

Cowden disease is a phacomatosis characterized by pathognomonic dermatological findings, multiple hamartomas, and a high risk of breast, thyroid, and endometrial carcinomas. Lhermitte–Duclos disease, or dysplastic cerebellar gangliocytoma, is a hamartoma associated with Cowden disease that can cause symptoms and signs of mass effect in the posterior fossa and lead to hydrocephalus, brain herniation, and death, if not treated. The prognosis for patients with LDD has improved markedly with advances in neuroimaging, particularly MR imaging.

Because of the need to screen affected patients for malignant lesions and provide genetic counseling, neurosurgeons need to be aware of the association between LDD and Cowden disease. Adult-onset LDD is now considered pathognomonic for Cowden disease (Table 1). In this review we focus on recent advances in imaging and the molecular biology of LDD, and we add another case to the literature.

Abbreviations used in this paper: LDD = Lhermitte–Duclos disease; MR = magnetic resonance; mTOR = mammalian target of rapamycin; PIP2 = phosphatidylinositol 4,5-bisphosphate; PIP3 = phosphatidylinositol 3,4,5-trisphosphate.

CASE REPORT

History. This 17-year-old right-handed girl presented with a generalized seizure. Phenytoin and topiramate were prescribed, and these medications prevented further episodes. The patient had no history of headache or other neurological symptom, and had been accepted to a 4-year college at the time of her initial presentation. She had a self-reported history of abnormal menses attributed to an ovarian cyst. She was born at term, met developmental milestones early, and had no problems in school. Maternal family members had histories of breast carcinoma, thyroid tumors, and ovarian cysts.

Examination. The general physical examination showed an obese (150 kg) young woman with fine papules on the tongue. Neurological examination was remarkable for a head circumference of 64 cm, average intelligence with clear speech, flat optic discs, and no focal abnormalities. Cranial MR imaging demonstrated a nonenhancing mass of exaggerated folia typical of LDD in the right cerebellar hemisphere, with no hydrocephalus (Fig. 1). Over the next 6 months, the patient experienced progressive suboccipital
headaches that were exacerbated by coughing and straining and were associated with nausea. Mild right dysmetria and truncal ataxia also developed. Repeated MR imaging revealed progressive crowding of the cerebellar tonsils.

Operation and Postoperative Course. The patient underwent suboccipital craniectomy, C-1 laminectomy, resection of the right cerebellar lesion, and duraplasty. She experienced mild respiratory difficulties in the early postoperative period that were attributed to her obesity. Her headaches disappeared and she completed her 1st year of college on schedule. Her dysmetria resolved within 3 months, and her truncal ataxia was gone by 1 year. After 4 years of follow-up visits, no sign of recurrence of the LDD has been observed. Additional systemic evaluation demonstrated a dermoid of the right orbit and intestinal polyps.

Patients With LDD Previously Reported at Case Western

Five patients with LDD and Cowden disease previously treated at Case Western Reserve have been reported. This sixth patient presented to us in 2001. In addition to the pathognomonic criteria of LDD and mucocutaneous lesions, she had a major criterion (macrocephaly), two minor criteria (ovarian cyst, intestinal polyps), and a family history that was suggestive of Cowden disease. All six patients in our series had symptomatic LDD, and they also had Cowden disease; these included a 9-year-old girl who underwent multiple resections for LDD before the age of 13 years, and who also met multiple systemic criteria for Cowden disease.

DISCUSSION

Lhermitte–Duclos Disease

The influence of modern imaging and surgical techniques on the prognosis for patients with LDD is noteworthy. Lhermitte and Duclos first described the cerebellar dysplastic gangliocytoma in 1920. They reported on a 36-year-old man who suffered occipital headaches and diminished hearing on the left side that was progressive over 10 months. During the few weeks before his presentation he suffered paroxysmal vertigo with recurrent falls, gait ataxia, disorientation, and memory deficits. At the time of admission, he exhibited confusion, disorientation, dysarthria, nystagmus, and cerebellar ataxia. His condition deteriorated and he died.

As recounted in Nowak and Trost, the first surgery attempted for LDD was performed in 1930 by Bielschowsky and Simons. The patient was a 20-year-old woman who presented with 2 years of progressive symptoms. She died during surgery before the dura mater was opened. The first successful surgery for LDD was performed in 1937 in a 34-year-old man who had experienced intermittent symptoms for 6 years. By 1955, only three patients had survived surgery for LDD. One third of the approximately 90 patients with LDD reported before 1994 died of complications of their disease. Approximately 220 patients with LDD have now been reported in the literature.

Neuroimaging in LDD. Modern neuroimaging, particularly the MR imaging modality, has greatly facilitated the diagnosis and care of patients with LDD. An MR image typically demonstrates the nonenhancing gyriform patterns of enlargement of cerebellar folia. Detailed images suggest the atrophic white matter, thickened granule cell layer, and enlarged molecular layer with excess myelinization. The T2-weighted images typically demonstrate a hypointense lesion with little or no enhancement, although patchy enhancement has been reported in five patients. The T2-weighted images demonstrate a well-circumscribed, high-intensity lesion with a “tiger-stripped” pattern. Lesions are hyperintense on diffusion-weighted images, and isointense to the normal cerebellum on apparent diffusion coefficient maps. The unique MR imaging pattern may be diagnostic and can obviate the need for a biopsy procedure in asymptomatic patients. Magnetic resonance imaging is also useful for preoperative planning and as an aid for determining the extent of the resection. Although the pattern for LDD is almost unique, in one case a medulloblastoma mimicked the typical findings of LDD on MR images obtained in an 18-month-old boy. This lesion, however, was somewhat atypical in that it demonstrated contrast enhancement and significant extension into the contralateral cerebellar hemisphere.

TABLE 1

<table>
<thead>
<tr>
<th>Criteria for diagnosis of Cowden disease*</th>
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<tbody>
<tr>
<td>pathognomonic</td>
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<tr>
<td>adult LDD</td>
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<tr>
<td>mucocutaneous lesions</td>
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<tr>
<td>facial trichilemmomas</td>
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<tr>
<td>acral keratoses</td>
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<tr>
<td>papillomatous papules</td>
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<tr>
<td>macusal lesions</td>
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<tr>
<td>major</td>
</tr>
<tr>
<td>breast cancer</td>
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<tr>
<td>thyroid cancer</td>
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<tr>
<td>macrocephaly</td>
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<tr>
<td>endometrial cancer</td>
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<tr>
<td>minor</td>
</tr>
<tr>
<td>noncancerous thyroid lesions</td>
</tr>
<tr>
<td>cognitive delay (IQ ≤75)</td>
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<tr>
<td>gastrointestinal hamartomas</td>
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<tr>
<td>breast fibrocytic disease</td>
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<td>lipomas</td>
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<tr>
<td>fibromas</td>
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<tr>
<td>genitourinary tumors (renal cell cancer)</td>
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<tr>
<td>genitourinary manifestations</td>
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<tr>
<td>uterine fibroid tumors</td>
</tr>
<tr>
<td>working diagnosis w/ no family history</td>
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<tr>
<td>mucocutaneous lesions alone</td>
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<tr>
<td>≥6 facial papules, of which ≥3 must be facial papules plus oral mucosal papillomatosis, or oral cutaneous papillomatosis &amp; acral keratosis, or ≥6 palmpoplantar keratoses</td>
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<tr>
<td>2 major criteria</td>
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<tr>
<td>1 major &amp; 3 minor criteria</td>
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<tr>
<td>4 minor criteria</td>
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<tr>
<td>working diagnosis in a family w/ 1 person in whom Cowden disease was diagnosed</td>
</tr>
<tr>
<td>pathognomonic criteria</td>
</tr>
<tr>
<td>1 major criterion</td>
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<tr>
<td>2 minor criteria</td>
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<tr>
<td>history of Bannayan-Riley-Ruvalcaba syndrome†</td>
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</table>

* Adapted from the National Comprehensive Cancer Network Guidelines, version 1.2006 (10/25/05). Abbreviation: IQ = intelligence quotient.
† This autosomal-dominant syndrome is also caused by FTO mutations (see Eng, 2003), and is characterized by macrocephaly, lipomatosis, hemangiomatosis, and speckled penis (see Gorlin, et al.).
Other modalities may also be helpful in the diagnosis of LDD. In a case report published by Nagaraja, et al., MR spectroscopy in two patients demonstrated reduced $N$-acetylaspartate/choline and $N$-acetylaspartate/creatine ratios compared with normal cerebellar tissue in eight control volunteers. Peaks attributed to lactate were also present. These findings are consistent with the hamartomatous nature of these lesions. Positron emission tomography scans obtained with the contrast agents $[^{18}F]$2-fluoro-2-deoxy-D-glucose and $[^{11}C]$-labeled methionine to measure glucose and protein metabolism have supported the theory that LDD increases metabolism similar to high-grade tumors. By contrast, a positron emission tomography study performed in other patients with LDD in which $[^{15}O]$-labeled water was used suggested that the metabolic rate of oxygen in LDD was similar to that in the normal cerebellum. Technetium-99m ethyl cysteinate dimer single-photon emission computerized tomography images in two patients with LDD demonstrated hyperactivity, suggesting that the LDD lesions are metabolically active, with a blood–brain barrier similar to normal tissue.

Screening with MR imaging to detect intracranial pathological lesions is likely warranted in most patients in whom Cowden disease has been diagnosed. In 20 patients with Cowden disease diagnosed by dermatologists, cranial MR imaging revealed that three had LDD, one had a meningioma, and six had vascular malformations (cavernous angiomas or venous angiomas). Conditional mice mutants (see later discussion) have shown that normal function of PTEN, the tumor suppressor gene for Cowden disease, is essential for formation of the vascular system. Thus, the high prevalence of vascular lesions found incidentally in patients with Cowden disease is not surprising.

**Pathological Features of LDD.** A lesion associated with LDD is a nonneoplastic mass composed of cerebellar folia expanded by hypertrophic neurons of the internal granule cell layer. The abnormal folia may not be present on the surface, and typically are paler than normal cortex. At surgery the margins between the lesion and the normal cerebellum are often indistinct, and transitional areas are often seen. Microscopic examination shows massive replacement and expansion of the internal granule cell layer by large hypertrophic neurons with vesicular nuclei and prominent nucleoli. The outer molecular layer is widened by the abundant, enlarged, irregularly myelinated axons from hypertrophic granule cells. There is loss of Purkinje cells and white matter, and no mitosis or proliferation is observed. In contrast to a glioma with diffuse infiltration, the hypertrophic neurons of LDD are larger, more rounded, more uniform, and appear in clusters.

**Cowden Disease**

In 1991 Padberg recognized that LDD is a manifestation of Cowden disease. Lloyd and Dennis named Cowden disease for Rachel Cowden, the first patient with this ha-
martoma/cancer syndrome, which they reported in 1963. She had multiple mucocutaneous abnormalities and died of infiltrating ductal carcinoma of the breast at 30 years of age. Because of the high risk of systemic cancers in patients with Cowden disease, it is imperative that they undergo appropriate screening measures. For example, women with this syndrome have a 25 to 50% lifetime risk of breast cancer, and in all patients with Cowden disease there is a 10% lifetime risk that epithelial thyroid cancer will develop. Approximately 90% of patients in whom Cowden disease develops manifest its clinical findings by 20 years of age.

Germline mutations in the gene PTEN at locus 10q23.2 have been identified as the major susceptibility gene for Cowden disease. Approximately 80% of patients with Cowden disease have a germline mutation of the PTEN gene, and another 10% harbor mutations in its promoter region. Approximately one half of the cases of Cowden disease are familial and one half are spontaneous, similar to the proportions in other phacomatoses caused by tumor suppressor genes. Other PTEN-related hamartomatous tumor syndromes in addition to Cowden disease include Bannayan-Riley-Ruvalcaba, Proteus, and Proteus-like syndromes.

Molecular Biology of PTEN

The PTEN gene was originally cloned as a tumor suppressor in a glioma. Somatic mutations of PTEN have been associated with glioblastoma, as well as melanoma and endometrial and prostate cancers. Heterozygous loss of Pten in mice produces an increase in cancer. The PTEN gene encodes a major lipid phosphatase for the phosphatidylinositol 3–kinase pathway (Fig. 2). The PTEN protein dephosphorylates PIP and PIP. Also, PTEN opposes the phosphatidylinositol 3–kinase pathway, inhibits formation of phosphorylated Akt, a serine/threonine kinase, and thus increases apoptosis. If PTEN is not present, unrestrained growth results in tumors. Most patients with LDD appear to have a germline loss of one PTEN allele and suffer loss of the remaining PTEN allele at some point, which allows abnormal growth of the granule cells.

Recent genetic models of LDD have clarified some of the controversies regarding the unusual lesions associated with this disease, including whether they are tumors or hamartomas. Mice with PTEN completely removed from the germline do not survive embryogenesis, impairing investigation of the role of the gene in specific cell populations. Studies in which conditional mouse mutants with the Cre-loxP system are used bypass this difficulty by deleting PTEN selectively in cells that have a specific gene promoter activated relatively late in development. Conditional mouse mutants of PTEN using the nestin promoter in neural precursor cells resulted in animals with disorganized brains containing hypertrophic neurons, and these mice died shortly after birth. Two models of PTEN deletion in which the glial fibrillary acidic protein promoter was used were published in the same journal issue. Interestingly, glial fibrillary acidic protein is characteristic of astrocytes, but the mutant mice showed deletion of PTEN in predominately granule cell neurons in the cerebellum and in dentate gyrus neurons in the hippocampus (PTEN was not deleted in astrocytes). The phenotype of these mutants was similar to LDD, with the same pathological findings in the cerebellum. No difference in proliferation or apoptosis was found.

Partial loss of PTEN expression in neural precursor cells alters migration and survival, but not proliferation. A downstream effector of the PTEN/Akt pathway is mTOR. In PTEN conditional mutant mice treated with systemic administration of CCI-779, an inhibitor of mTOR, neuronal hypertrophy did not occur. Studies of human LDD demonstrate that the PTEN/Akt pathway behaves as predicted by the models in mice. Immunohistochemical staining in tissue from lesions obtained in patients with LDD demonstrates decreased expression of PTEN in hypertrophic neurons, accompanied by increased expression of P-Akt and activation of mTOR. Abnormal hypertrophic neurons in LDD are large but do not demonstrate excess proliferation or impaired apoptosis characteristic of tumors. Together, these results argue that LDD is a hamartoma and not a tumor. They also explain the relatively slow growth of the lesion and its likelihood of recurrence in some patients.

Cases of LDD in Children

All six patients in our series at Case Western Reserve who had symptomatic LDD also had Cowden disease, including a 9-year-old girl who underwent multiple resections for LDD before the age of 13 years, and the 17-year-old girl presented in this paper. We found reports in the literature that LDD has been diagnosed in approximately 14 patients who were 17 years old or younger (range 11 months–17 years), including the patient reported in this study. Of these 14 patients with LDD, three received diagnoses of Cowden disease (and this paper), eight had no signs of Cowden disease, and for three the systemic history and examination of nonneurological symptoms were not mentioned, precluding the diagnosis of Cowden disease. Many of the manifestations of Cowden disease may not appear until the second or third decade of life, precluding early diagnosis. Interestingly, all three of the 18 patients with LDD but without PTEN mutations reported by Zhou, et al., were children. Another child with LDD who underwent resection at 13 years of age and regular follow-up visits for an additional 13 years had no other manifestation of Cowden disease, and furthermore had intact PTEN pathway expression. Tissue samples obtained from the lesion in this child, however, demonstrated excess levels of mTOR pathway expression, suggesting that in patients with no loss of PTEN expression, LDD may arise from aberrant expression of the downstream effector mTOR. Such patients may not be at risk for the other tumors associated with Cowden disease. Within the next several years, further understanding of the biology of PTEN and its relationship to LDD should allow greater accuracy in making the diagnosis of Cowden disease in patients with LDD. Reliable and accurate diagnosis will allow cancer surveillance and genetic counseling when necessary, and should clarify which patients are at higher risk for systemic cancer.

CONCLUSIONS

The diagnosis of LDD, or dysplastic cerebellar gangliocytoma, can now frequently be made using MR imaging, and this advance has markedly improved the prognosis for the disease. Some patients with LDD become symptomatic...
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and require resection of the cerebellar mass. The lesion can recur, but does not transform into a more aggressive tumor. Recent studies of the biology of the PTEN pathway explain why LDD is a hamartoma, and not a tumor. These studies also explain why a small subset of patients with LDD may not be prone to Cowden disease. Until the biology of the PTEN pathway and its relationship to LDD and Cowden disease are better understood, we recommend that all patients with LDD be evaluated and followed for systemic cancers associated with Cowden disease.

References

Fig. 2. Schematic drawing showing that loss of function of PTEN activates the Akt pathway. Normally PTEN limits the phosphorylation of PIP₃ (PI(3,4,5)P₃). When PTEN is not present, PIP₃ activates phosphoinositide-dependent kinase-1 (PDK1), which phosphorylates Akt, a serine/threonine kinase also known as protein kinase B (PKB). Phosphorylated Akt (P-Akt) drives several cellular processes, including migration, proliferation, and survival, and leads to tumor formation if not controlled. In addition, phosphorylated Akt inhibits the tuberous sclerosis complex gene products TSC1/TSC2. Normally, TSC1/TSC2 inhibit mTOR and limit cell size. If loss of PTEN produces excess phosphorylated Akt, which in turn inhibits TSC1/TSC2, then mTOR is no longer suppressed. Excess mTOR in neurons results in uncontrolled cell growth, or the neuronal hypertrophy typical of LDD. Approximately 90% of patients with LDD have a mutation in PTEN or its promoters. Those patients without loss of PTEN function from a mutation may have aberrant activation of the downstream effector, mTOR. Treatment with CCI-779 inhibits mTOR and may have therapeutic potential as an adjunct to surgery. PI(4,5)P₂ = PIP₂.


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