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Case Report

A young Female of Cowden Syndrome Presenting with Lhermitte- Duclos Disease: A Case Study

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Abstract

Cowden Syndrome (CS) is a rare autosomal dominant inherited genetic disorder due to germline mutations in the phosphatase and tensing homologue (PTEN) tumor suppressor gene in chromosome 10 characterized by multiple hamartomata's lesions of ectodermal, mesodermal and endodermal origin. Lhermitte-Duclos Disease (LDD), or dysplastic gangliocytoma, which is a benign hamartomata's condition involving the cerebellum with less than 300 cases reported in the literature. Previous studies suggest an association between CS and LDD. We present here a case of a 28-year female patient presented at the emergency department of our hospital with severe headache associated with vertigo, vomiting & cerebellar ataxia. Papilledema was noted on fundoscopy. Non-attenuating hypodense mass lesion in posterior fossa was found in CT scan. MRI scan T1WI film revealed mixed intensity posterior fossa lesion and T2WI film revealed inhomogeneous hyperintense lesion with almost preserved cerebellar cortical striations. USG revealed numerous polyps in the gallbladder with cholelithiasis. Her facial skin has extensive trichilemmoma. Her symptoms improved after excision of posterior fossa lesion through suboccipital craniectomy and histopathology revealed dysplastic cerebellar gangliocytoma i.e., Lhermitte-Duclos disease. Using the Cleveland Clinic Adult Clinical Scoring for PTEN Testing, the patient had an 82-98% chance for a PTEN gene mutation. Finally, she along with her family was adequately counseled and was advised for regular screening and monitoring.

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Introduction:

Multiple hamartoma syndrome eponym as Cowden syndrome (CS) is a rare autosomal

dominant disorder which is a cancer predisposition syndrome. It is characterized by

multiple hamartomas in a variety of tissues from all three embryonic layers. It is due to the germline mutations of the PTEN tumor-suppressor gene[1,2]. It belongs to PTEN hamartoma tumor syndrome which also include Lhermitte Duclos Disease (LDD), Bannayan-Riley-Ruvalcaba Syndrome, Proteus syndrome, Proteus like Syndrome, SOLAMEN syndrome, macrocephaly/autism syndrome, and juvenile polyposis syndrome[2,3].

[Figure 1: Cowden syndrome: An autosomal dominant (AD) disease; each child with an affected AD disease has a 50% possibility of inheriting the same disease. Image Courtesy: National Institute of Health (NIH), US.]

Lhermitte–Duclos disease is a rare disorder characterized by slowly progressive unilateral dysplastic gangliocytoma of cerebellar cortex[4,5].

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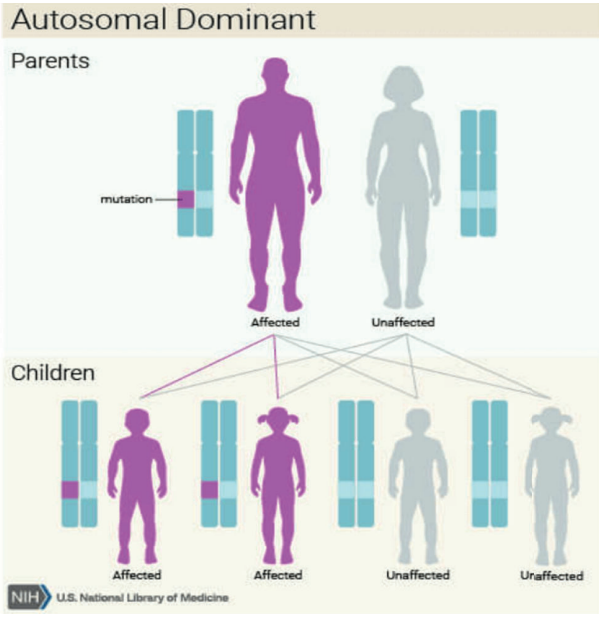


However, adult-onset Lhermitte-Duclos disease (LDD) and Cowden syndrome (CS) are considered a single phakomatosis that belongs to PTEN hamartoma tumor syndrome (PHTS)[6]. In a case series of 18 patients with LDD, 11 were diagnosed as CS[6].

Adult LDD is considered as one of the pathognomonic criteria for diagnosing CS, along with mucocutaneous lesions, facial trichilemmomas, acralkeratoses and papillomatous papules[1,7].

The diagnostic criteria for Cowden syndrome are as follows[1]:

- Pathognomonic criteria
  - Adult Lhermitte-Duclos disease (LDD) (cerebellar tumors)
  - Mucocutaneous lesions
  - Facial trichilemmomas
  - Acralkeratoses
  - Papillomatous papules

Major criteria

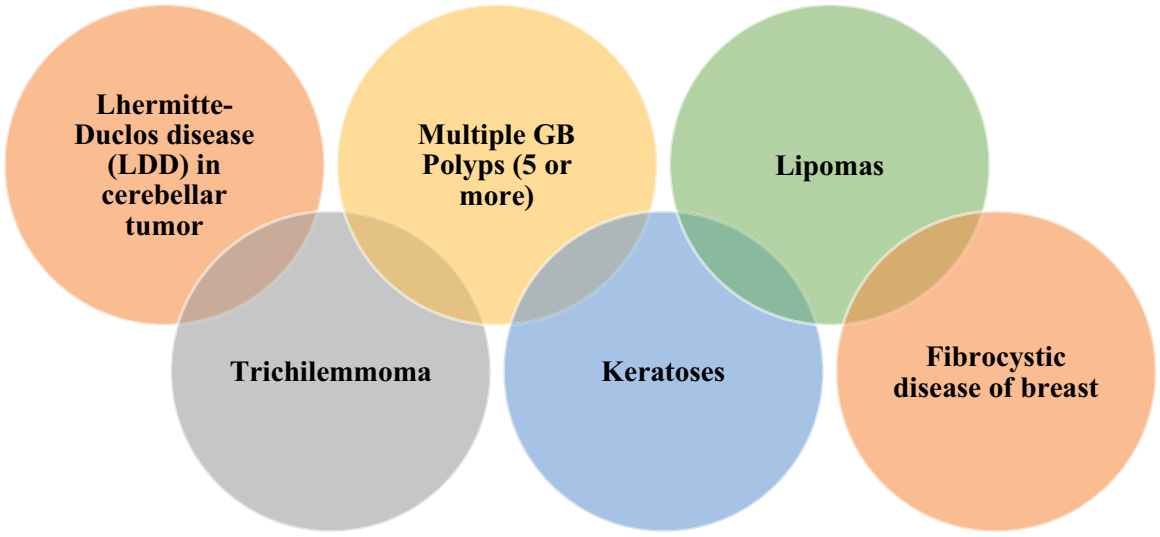
- Breast carcinoma
- Non-medullary thyroid carcinoma
- Macrocephaly (megalocephaly) (P97th percentile)
- Endometrial carcinoma

Minor criteria

- Other thyroid lesions (e.g. adenoma, multinodular goiter)
- Mental retardation (IQ < 75)
- GI hamartomas
- Fibrocystic disease of the breast
- Lipomas
- Fibromas
- GU tumors (especially renal cell carcinoma); GU structural manifestations
- Uterine fibroids

Among these, our patient had cerebellar tumor, facial trichilemmomas, keratoses and also a number of minor criteria.

Besides, Lhermitte-Duclos disease is a rare condition, first recognized in 1920 by Lhermitte and Duclos [8]. It is a very rare type of posterior cranial fossa tumor



[Figure 2: Some suggestive features of the presented patient to Cowden Syndrome]

Table-I

Summary table of Lhermitte-Duclos disease (LDD)

Etiology	PTEN mutation that leads to dysplastic gangliocytoma of the cerebellum.
Incidence	Highly rare- only less than 300 known cases of LLD have been published in PubMed-indexed literature as of July 2022.
Gender ratio	No gender predilection
Age predilection	Most frequently diagnosed in 2nd or 3rd decade
Risk factors	Genetic correlation between LDD and Cowden syndrome, an autosomal dominant syndrome characterized by multi-organ hamartomatous tumors
Treatment	Observation, unless mass effect symptoms warrant surgical intervention. Complete surgical resection is curative.
Prognosis	This is a slow-growing, benign tumor, so the prognosis is generally favorable.
Findings on imaging	(MRI is usually sufficient for diagnosis*)Gross: focal, well-circumscribed lesion restricted to one of the cerebellar hemispheres with folia hypertrophy. Widened cerebellar folia with apparently preserved striations; called corduroy/ laminated appearance.T1: hypointense signalT2: “tiger stripes” appearance of alternating low and high signal or hyperintense with apparently preserved cortical striations.

[*Carter Et al [12] were the ones to establish a preoperative diagnosis based on MRI first.]
[Reference: 9, 11, 12]

that can either arise as an isolated condition or with association with CS [9]. A literature search in July 2022 resulted with less than 300 confirmed cases. Clinical symptoms generally arise from/are related tomass effect changes in the posterior fossa and can include headache, nausea, and visual disturbances and sometimes, might cause blindness too.These early symptoms can be controlled by sometimes through shunt placement (e.g. Ventriculo-peritoneal shunting) which can help with the release of CSF blocking. The severity of symptoms can vary depending on the size of the lesion, and patients with isolated LDD may be asymptomatic for years. If the lesion grows large enough, patients may also exhibit signs of cerebellar dysfunction and obstructive hydrocephalus [10]. Surgery is considered at that time to resect that abnormal growth.Table 1 gives a brief summary of LDD.

Case Presentation

A 28-year-old female patient presented at the emergency department of Dhaka Medical College

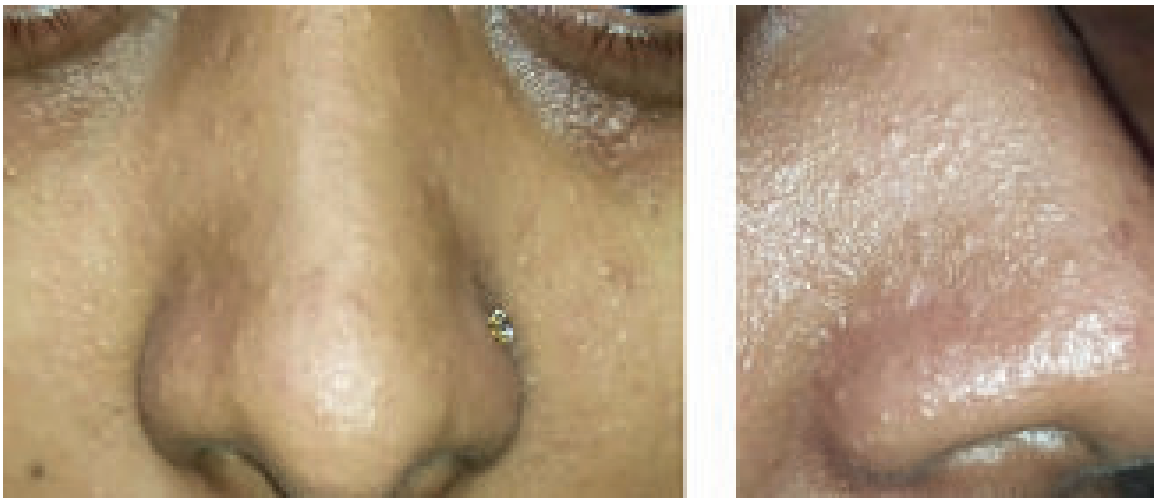


Fig.-3: *Picture of face showing Trichilemmoma*

Hospital on November 2020 with a severe headache associated with vertigo and vomiting. Neurological assessment revealed average intelligence and marked cerebellar ataxia. Papilledema was noted on fundoscopy. CT scan revealed mildly heterogeneously enhancing mass lesion in right cerebellar hemisphere with significant compression over pons and causing tri ventriculomegaly. After primary resuscitation, detailed history and examination was carried out and previous records were checked. Clinical examination revealed mild anemia and firm flat topped brownish papules over face, and hyperkeratosis over several areas in the body. Multiple lipomas were palpated in limbs and torso. On breast examination, lumps palpated on both sides which later investigated with USG revealed Fibrocystic Disease. Thyroid was normal. USG of abdomen was done previously as she complained of occasional abdominal pain which revealed cholelithiasis with multiple gallbladder polyps. As genetic testing is readily not that available and also very expensive in Bangladesh, the striated appearance of the affected side of cerebellum, seen through MRI, is subjected to appear as one of the strongest indicators of LDD here. The patient was monitored closely to figure out whether to receive conservative management and annual screening to measure the growth of that hamartoma or to go for surgery to alleviate mass effects or complications. Here, our patient underwent excision of the posterior fossa lesion through suboccipitalcraniectomywhich resulted in improvement of cerebellar symptoms. Subsequent histopathology revealed derangement of the normal laminar cellular organization of the cerebellum. There was thickening of the outer molecular cell layer, loss of the middle Purkinje cell layer, and infiltration of the inner granular cell layer with dysplastic ganglion cells of various sizes and abundance of fibrillary astrocytes. These appearances went in favor of dysplastic gangliocytoma or LDD (differential diagnosis: fibrillary astrocytoma). All these clinical findings lead to diagnosis of Cowden syndrome.

The patient is on our follow-up. She developed hypothyroidism 2 years later in 2022 as diagnosed in a follow-up and taking treatments accordingly.

Cowden syndrome (CS) is an often difficult-to-recognize hereditary cancer predisposition syndrome caused by mutations in phosphatase and tensin-homolog deleted on chromosome 10 (PTEN)[13]. We

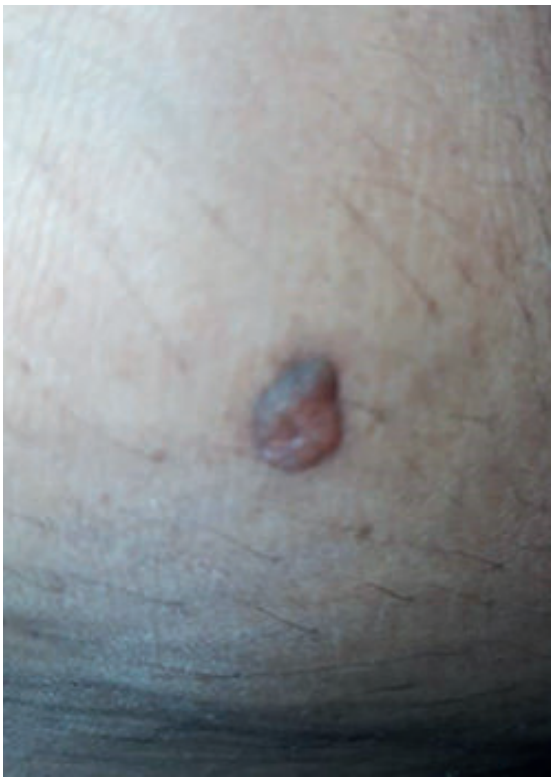


Fig.-4: *Trichilemmoma of the thigh]*

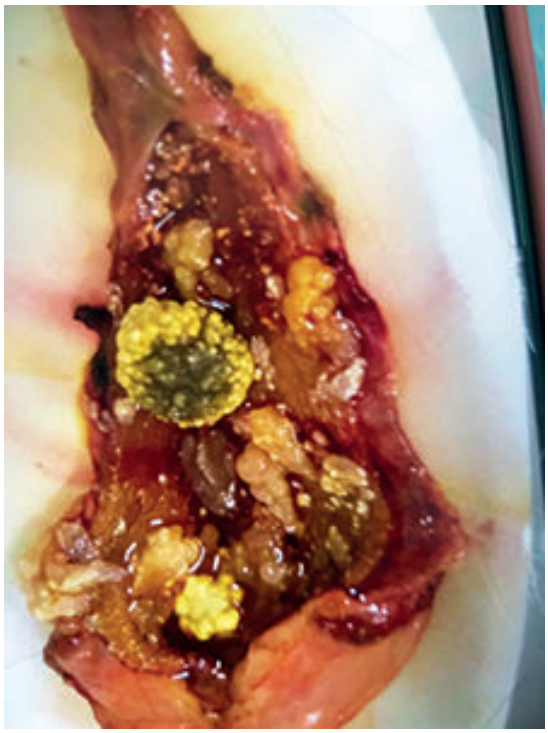


Fig.-5: *Multiple Gallbladder polyps (5 or more) with pigmented stones after cholecystectomy.]*

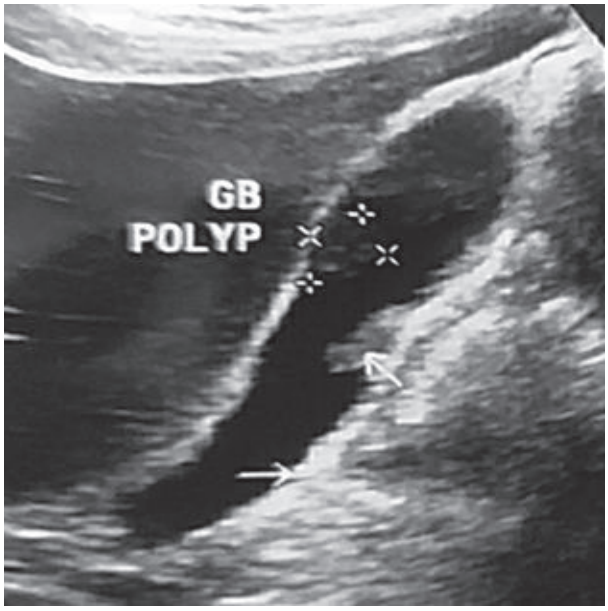


Fig.-6: *Multiple GB Polyps with Cholelithiasis; Two mobile bright echogenic structures in the lumen of gallbladder casting distal acoustic shadows (Larger one 1.5X .6 cm). Numerous Soft tissue echogenic structures without acoustic shadows are seen adherent with both anterior and posterior wall.]*

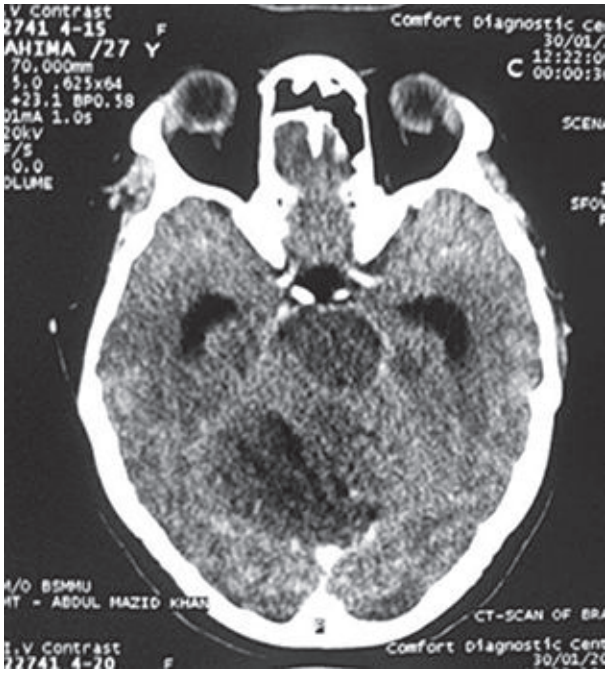


Fig.-7: *Contrast enhanced CT scan of brain axial image showing Ill-defined hypodense area with mild heterogeneous enhancement in right cerebellum involving middle cerebellar peduncle having perilesional oedema and mass effect compressing pons, effacement of 4th ventricle resulting mild dilatation of both lateral and 3rd ventricles.]*

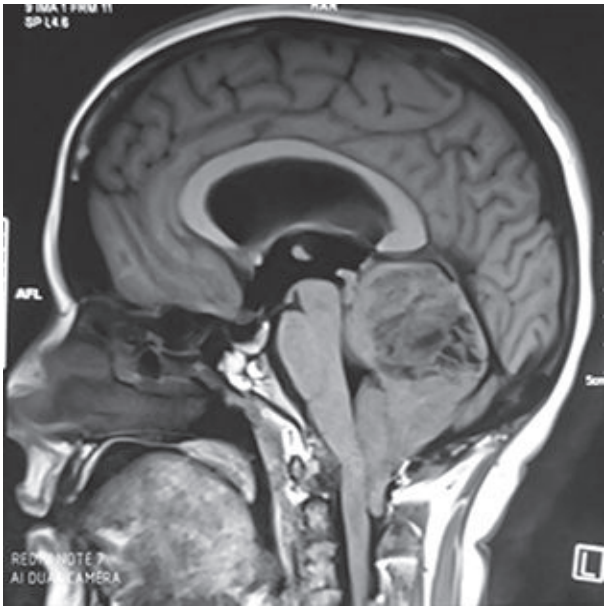


Fig.-8: *MRI of Brain sagittal T1WI: mixed intensity Right cerebellar SOL exerting significant mass effect causing tri ventriculomegaly. Suggestive of low-grade glioma; Differential – LDD; which was later confirmed histopathologically to be LDD.]*

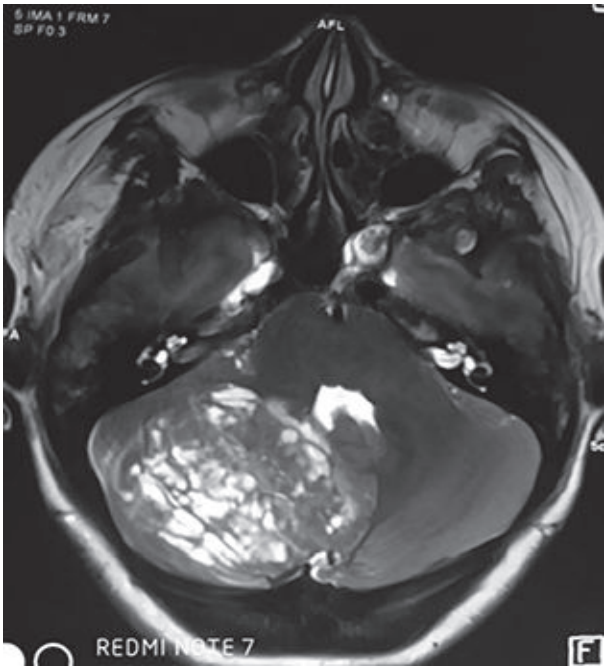


Fig.-9: *Contrast enhanced MRI scan of brain axial image showing mild heterogeneously enhancing, tigroid or striated mass lesion on right cerebellum involving middle cerebellar peduncle having perilesional oedema and mass effect compressing pons, effacement of 4th ventricle resulting tri ventriculomegaly; suggestive of low-grade glioma. Differential – LDD, (which was later confirmed in histopathology to be LDD).]*

used Cleveland Clinic Adult Clinical Scoring for PTEN Testing (can be accessed here: http://www.lerner.ccf.org/gmi/ccscore/) [14]. It showed the patient had an 82-98% chance for a PTEN gene mutation. In a developing country where genetic testing is not yet widely available, the scoring system aided us to do genetic counseling for a predisposition for cancer. Since this is a genetic disorder and can be associated with other malignancy, our patient along with her family was adequately counseled and was advised for regular screening and monitoring.

Conclusion:

It is captivating how a single genetic mutation can lead to a broad variety of abnormalities, as seen in our case, necessitating surgery, family counseling and monitoring the patient carefully. While genetic testing for such disorders is not possible here in most cases, thorough clinical and proper lab investigations should be done as early as possible to lessen the complications and detect or exclude associated malignancies that might appear someday in future.

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