Cerebellar Dysplastic Gangliocytoma as the First Presentation of Cowden Syndrome

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Abstract

Cowden syndrome is a rare autosomal-dominant disease characterized by multisystem hamartomas usually affecting the skin, thyroid gland, breast, and gastrointestinal tract; these hamartomas tend to undergo malignant transformation in various tissues. We describe a 32-year- old woman who presented with a progressive headache, neck pain, nausea, vomiting, transient loss of vision, dizziness, and unsteady gait during the previous 2 months; she had one episode of a seizure and a previous history of an ovarian cyst manifesting as abnormal menses. Brain magnetic resonance imaging (MRI) revealed a left cerebellar mass with features suggestive of dysplastic gangliocytoma with obstructive hydrocephalus in addition to multiple meningiomas. Imaging features raised the suspicion of Cowden syndrome (CS). Thus, the patient underwent suboccipital craniotomy for resection of the left cerebellar mass; pathological and immunohistochemical examination confirmed the diagnosis of CS. Most cases found in the literature reported delayed diagnoses of this condition; however, our patient?s peculiar MRI features facilitated early diagnosis and likely prevented or delayed possible complications. This case highlights the clinical manifestations and diagnostic criteria of CS even in the absence of mucocutaneous manifestations.

Index terms—
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1 I. Introduction

owden syndrome (CS), which was first described by Lloyd and Dennis in 1963 and is also known as PTEN hamartoma tumor syndrome, is a rare autosomal-dominant disease characterized by multisystem hamartomas usually affecting the skin, thyroid gland, breast, and gastrointestinal tract [1]. Germline mutations in the PTEN gene are thought to constitute the etiology of this syndrome [2]. Although hamartomas are the most common manifestation of this disease, CS has also been linked to many types of cancers such as those of the breast,

thyroid, and uterus [2]. Other less common types of cancer include colorectal, kidney, and skin cancers [2,3].In rare cases, benign brain tumors can occur; these have been linked to a small percentage of individuals with intellectual disabilities [2]. In this study, we describe a 32-year-old woman with an early manifestation of CS; our particular case highlights the clinical manifestations and diagnostic criteria of CS even in the absence of mucocutaneous manifestations.

2 II. Case Report

A 32-year-old Saudi woman presented to the neurology clinic with a progressive headache, neck pain, nausea, vomiting, transient visual loss, dizziness, and an unsteady gait for the past 2 months. She had also experienced one episode of a seizure and had a history of an ovarian cyst manifesting as abnormal menses. The patient had no notable family history of malignancy; she had undergone resection of a mass that was diagnosed as a lipoma in her lower back two years prior. Physical examination revealed conjunctival pallor, diffuse thyroid goiter, pectus excavatum, and a scar in her left lower back due to the aforementioned resection. No cutaneous or mucosal abnormalities were noted.

Initial blood work was normal except for a hemoglobin level of 9g/dL and a low mean corpuscular volume (70 fL). Thyroid function tests, erythrocyte sedimentation rate, C-reactive protein, and lactate dehydrogenase were all normal. Magnetic resonance imaging (MRI) of the brainrevealed a left cerebellar expansile mass with widened cerebellar folia that caused a compression effect over the fourth ventricle, with supratentorial tri-ventricular hydrocephalus consistent with dysplastic gangliocytoma (Figure **??**A and 1B). Furthermore, multiple dural-based intensely enhancing masses were noted in the right temporal lobe and the retroclival regions; this was consistent with multiple meningiomas (Figure2). The patient underwent suboccipital craniotomy for resection of the left cerebellar lesion. Immunohistochemistry was positive for synaptophysin, and molecular genetic testing confirmed the presence of a PTEN10q23.31 mutation. Full sequencing of PTEN revealed a heterozygous G to T mutation on exon 7. The final diagnosis was CS.

Next, a full screen for other possible manifestations of her disease was performed; this revealed hypervascular multinodular goiter on thyroid ultrasonography and a thinning of the endometrial stripe (<2mm) on pelvic ultrasonography. Breast ultrasonography revealed evidence of fibrocystic disease, and breast MRI was highly suggestive of 'breast imaging-reporting and data system (BI-RADS)' IV. A true cut biopsy from both breasts confirmed the diagnosis of sclerosing intraductal papilloma, while a colonoscopy revealed the presence of extensive hyperplastic rectal polyps. Further evaluation of the gastrointestinal tract was performed using a barium study, which showed nodular thickening of the mucosal fold in the terminal ileum. Lastly, prophylactic mastectomy and rectal polypectomy were discussed and recommended to the patient, and the importance of follow-up and continuous surveillance was emphasized. The patient is currently performing well with no neurological symptoms.

3 III. Discussion

CS is a rare autosomal dominant disease that is mainly characterized by hyperplastic hamartomas and tumoral lesions affecting multiple organs [1,4]. Furthermore, this disease can predispose patients to multiple cancers; it is usually diagnosed during the third decade and is predominant in women [5]. Ectodermal, endodermal, and mesodermal alteration is a known feature of this syndrome,which reflects the range of affected organs [5]. The most commonly affected organs in order of frequency are the skin, mucus membranes, breast, bone, gastrointestinal tract, thyroid, genitourinary system, and central nervous system (CNS) [5,6,7].

Numerous CNS tumors have been linked to the same gene mutation found in CS, most of which were discovered in asymptomatic patients [8]; CNS manifestations are only observed in one-fifth of patients with CS [5,8]. A possible link between PTEN mutations and developmental delay or mental retardation has been reported (reviewed in [8]). Another CNS manifestation is macrocephaly, which is observed in 80-100% of patients with PTEN mutations [8]. Autism spectrum disorders have also been linked to CS [8]; furthermore, dysplastic gangliocytoma of the cerebellum,also known as Lhermitte-Duclos disease (LDD), is considered a pathognomonic feature of CNS manifestations of CS [7,8].

LDD is a rare, non-malignant, slow growing hamartoma that is commonly asymptomatic or exhibits relatively subtle cerebellar signs. If sufficiently large, however, symptoms may include headaches, visual problems, cerebellar ataxia, and signs of increased intracranial pressure [8]; these symptoms were apparent in our patient. LDDis usually diagnosed in the second or third decade of life; diagnosis of this disease in adulthood has been linked to CS more so than in children [8,10].The microscopic appearance of LDD usually manifests as disarrangement of the laminar cellular architecture of the cerebellum. Additionally, invasion of the inner granular layer of the cerebellum, loss of the middle Purkinje layer, and thickening of the outermost layer are observed. Radiographic features of LDD usually exhibit abnormalities in the tissues involving the cerebellar cortex, and usually only on one hemisphere (rarely both), with involvement of the vermis occasionally observed. Computed tomography may only show a nonspecific hypoattenuating cerebellar mass, and calcification may also be rarely observed. On MRI,the lesion is usually confined to one cerebellar hemisphere showing widened cerebellar folia with a striated tigroid appearance; enhancement of such lesions is rare.

In the present case, the clinical presentation of our patient together with MRI findings of a left cerebellar mass with obstructive hydrocephalus mandated surgical resection; this resection was complete, and no recurrence was

observed on MRI during the 3-year follow-up period. The retroclival and right temporal meningiomas did not undergo surgical intervention since the patient was asymptomatic with no mass effect noted over the adjacent intracranial structures.

Mucocutaneous manifestations are considered the most common signs of CS, and almost 100% of patients will have at least one type of manifestation. These may include facial papules (trichilemmomas), acral keratoses, papillomatous papules, mucosal papillomas, basal cell carcinoma, squamous cell carcinoma, and malignant melanoma [1,5]. Moreover, these manifestations are essential for the diagnosis of CS; however, they have very little malignant potential [1,3,8]. Despite the high prevalence of these manifestations in CS, our patient did not show any such mucocutaneous lesions.

CS is commonly associated with breast cancer; the lifetime risk of which is approximately 77% in patients with CS [8]. Furthermore, benign breast lesions are known to be a key diagnostic criterion for CS [2]; fibrocystic disease is found in 75% of all female patients with CS [8].Moreover, fibroadenomas and intraductal papillomas are also associated with CS [8]. Our patient was unique in that she had both fibrocystic disease and intraductal papilloma simultaneously. Moreover, the most frequent genitourinary tract features in women with CS are ovarian cysts, functional menstrual irregularities, leiomyoma, and endometrial cancer [5]. This was true in our patient, who reported irregular menstrual cycles in the previous two months.

The gastrointestinal tract is commonly involved in patients with CS, with a cumulative cancer risk in the colon, rectum, and (rarely) small intestines of 16% [8]; these lesions most commonly manifest as hamartomatous polyps [5,8].However, this was not the case for our patient, who had extensive hyperplastic rectal polyposis. Although most polyps do not carry a malignant potential, 13% of patients with CS who underwent colonoscopy were found to have colorectal cancer in one study [8].Moreover, our patient showed nodular thickening of the mucosal fold in the terminal ileum upon undergoing a barium study, suggesting the presence of small bowel polyps.

Other CS manifestations include diseases of the bone and thyroid [1,2,5]. Skeletal manifestations are observed in 37% of all patients with CS [5]; these include macrocephaly, polydactyly, syndactyly, bone cysts, and kyphoscoliosis [5]. Thyroid diseases include multinodular goiter, thyroiditis, and thyroid cancer [8]. Macrocephaly and bilateral thyroid lesions were noted at the initial presentation of our patient.

A provisional diagnosis of CS was made mainly based on the presence of LDD, thyroid disease, fibrocystic disease, gastrointestinal hamartomas, and lipoma [2,8]. Our patient's symptoms fulfilled the clinical criteria of the International Cowden Consortium [9], according to which one major criterion (any of: breast carcinoma, thyroid carcinoma, macrocephaly, and endometrial carcinoma) and three minor criteria (any three of: noncancerous thyroid lesions, IQ ?75, gastrointestinal hamartomas, lipomas, breast fibrocystic disease, uterine fibroids, fibromas, and genitourinary tumors or malformations) represent a diagnosis of CS. Most patients with CS have a germline in the tumor suppressor gene PTEN. Loss of function of PTEN contributes to cellular transformation, increasing the risk of cancer development, premature death, and resistance to chemotherapy and radiation. The presence of a PTEN 10q23.31 mutation was confirmed in our patient [9].

Management of patients with CS necessitates a multidisciplinary treatment and surveillance plan [2]. Full blood count, urinalysis, thyroid function test, and mammography are baseline studies required for CS diagnosis, and should be repeated as often as clinically necessary.

Frequent and thorough physical examinations are mandatory to detect any complications of this syndrome. Patient education regarding the possible signs and symptoms of cancer is crucial, as is emphasizing the importance of lifelong follow-up and genetic counseling as requires [3].

4 IV. Conclusion

Most patients with CS who were reported in the literature had delayed diagnoses. Although our patient did not have any mucocutaneous manifestations, which is the most common presentation of CS, the presence of left cerebellar LDD and multiple meningiomas on imaging were strong indicators of CS. This facilitated early diagnosis and may have served to prevent or delay any future possible complications.

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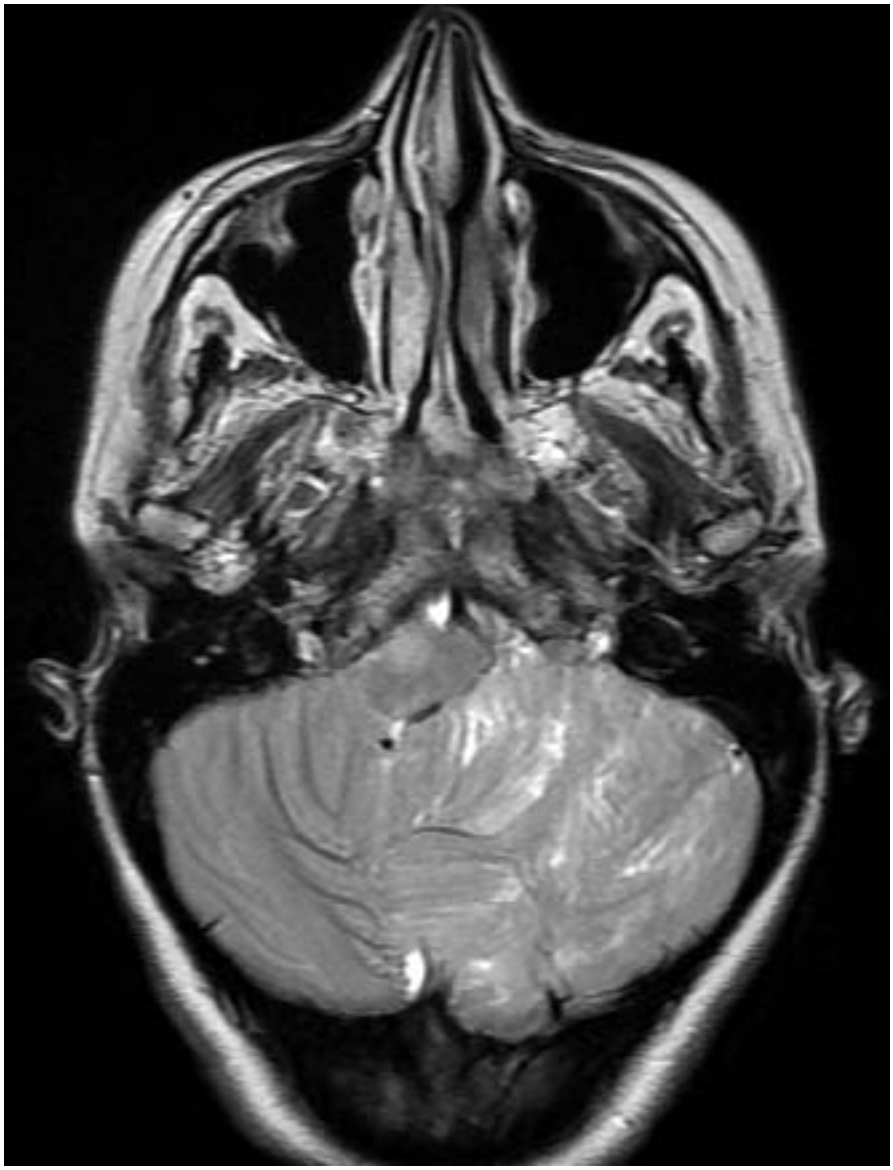

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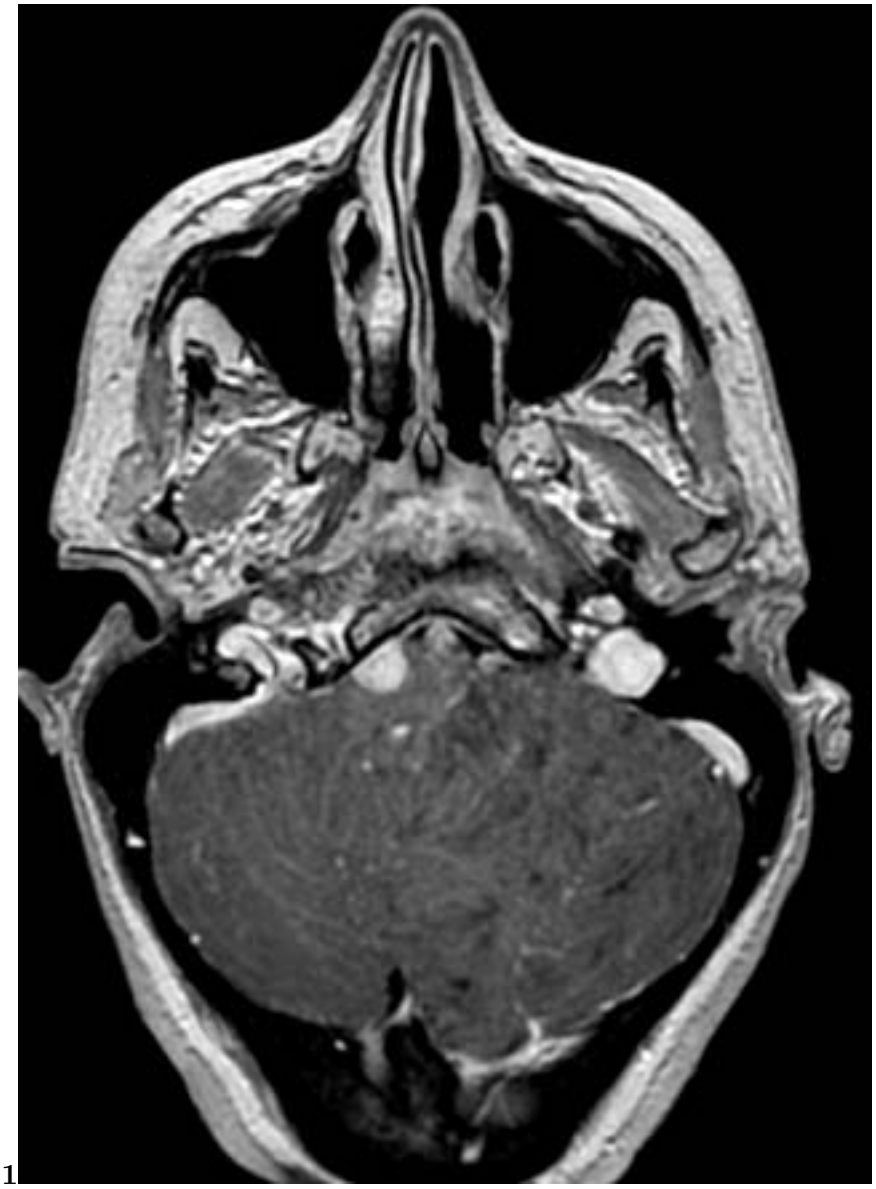
1B1 

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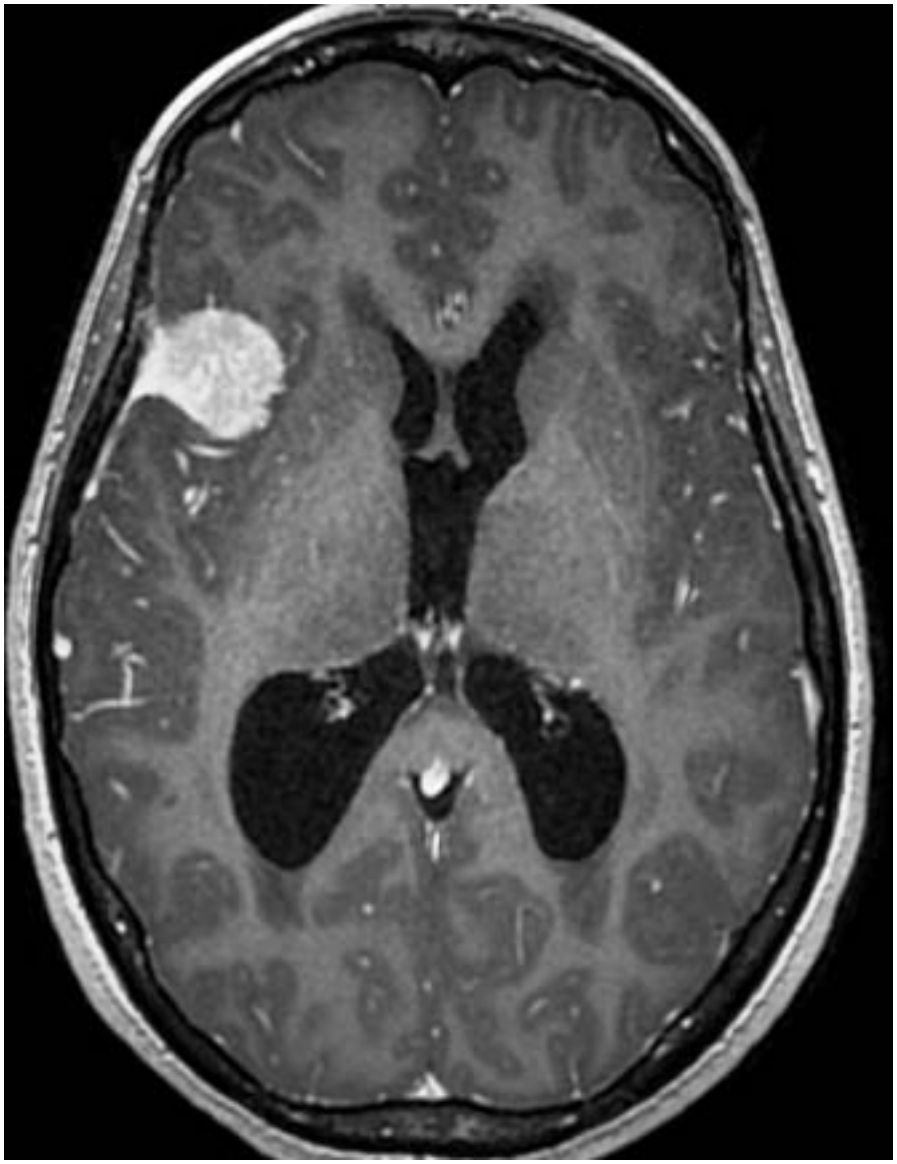

Figure 3:

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