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TUBEROUS SCLEROSIS PRESENTING WITH RETINAL ASTROCYTIC HAMARTOMA AND DYSPLASTIC CEREBELLAR GANLIOCYTOMA : A RARE NEURO-OPTHALMIC ASSOCIATION

Radiology

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ABSTRACT

Tuberous Sclerosis Complex is a rare genetic disorder of autosomal dominant inheritance. It is a neurocutaneous syndrome exhibiting multiple hamartomatous proliferations involving multiple organ system such as brain, kidney, heart, lungs, eyes and skin. Here, we present a case report of a 5 year old female patient with characteristic clinical and radiological features of Tuberosis Sclerosis Complex.

KEYWORDS

Genetic disorder, Tuberous sclerosis complex, Retinoblastoma, Dysplastic cerebellar gangliocytoma

INTRODUCTION:

Tuberous sclerosis/ Bourneville disease is a genetic disorder that affects cellular differentiation, proliferation and migration in early embryonic development, which subsequently leads to the formation of hamartomatous (benign tumors) lesions, which may affect virtually every organ system of the body. [1]

Tuberous sclerosis complex (TSC) is a rare disorder with heterogeneous presentation varying from severe mental retardation and incapacitating seizures to normal intelligence and an absence of seizure, often within the same family. It is due to inactivating mutation in one of the two genes, TSC1 encoding hamartin or TSC2 encoding tuberin[2,3]. The major neurological manifestations of Tuberous Sclerosis Complex are seizures, autism, developmental delay and behavioral and psychiatric disorder. Seizure is present in about 80-90% of patient which begins during the first year of life; varies from subtle focal seizure, infantile spasm, to generalized seizure [2,4]. Seizures are managed with an anticonvulsant medication like Vigabatrin for infantile spasm, Lamotrigine for generalized seizure[3]. But young children with TSC who have early onset of focal seizure or spasm, develops intractable seizures later that responds poorly to antiepileptic drug[1]. Those are candidates for alternative non-pharmacological treatment which includes vagus nerve stimulation, use of ketogenic diet and resective surgery [5]. TSC has dermatologic manifestations like hypomelanotic macules (90%), facial angiofibromas (75%), Shagreen patch (20 30%)[3] .

Lhermitte Duclos disease (LDD) or dysplastic cerebellar gangliocytoma is a rare disease of the cerebellar gangliocytoma is a rare disease of the cerebellum considered halfway between a glioma with low malignancy grade and a slow progressive malformative-dysplastic disorder. [6,7]

The prognosis is variable as it depends upon the system involved. Due to the wide spectrum of clinical manifestations, its diagnosis is often delayed. Here, we demonstrate a known case of tuberous sclerosis who referred with query of left eye retinoblastoma.

CASE REPORT:

A 5 year old female child from a nearby village referred in pediatric OPD with query of left eye retinoblastoma. She is a known case of tuberous sclerosis. No any fresh complaint at present.

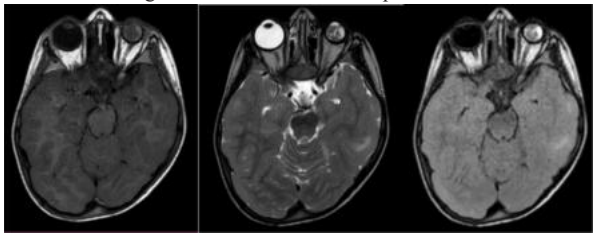
Upon inquiring her past medical history, she was born by LSCS & 3rd birth order & third degree consanguine marriage. No history of delayed cry. The indication for LSCS was cephalo-pelvic disproportion. However, her developmental milestones were delayed specially speech. Parents gave history of single episodes of seizure at 4 month of age & had been on Syrup oxcarbazepine 150mg & Syrup Levipil since then. Seizure free duration was more than 1 years. There was no history of seizure in family members. Immunization was incomplete till age.

EXAMINATION:

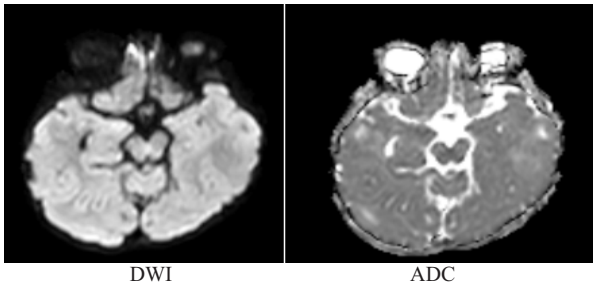
The child was examined in sitting position. She was active, conscious & well oriented and afebrile. Pulse was 112/min .Peripheral pulses was present. Respiratory rate was 20/ min. Dyspnea absent. SPO_2 96% on RA. No pallor, icterus, clubbing, oedema of foot, lymphadenopathy. Left eye has microphthalmia. Systemic examination findings was within normal limit.

Investigations:

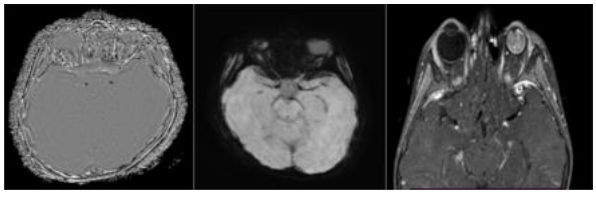
- CBC shows, 11 gm% Hb, 34.3% PCV, 11500TLC, 4.24 lac platelet & Blood group was AB+ve. Blood urea was 18, Sr. Creatinine 0.7, Sr. Bilirubin 0.4, SGOT 38, SGPT 10. HIV & HbsAg was non-reactive.
- 2D ECHO shows 60% LVEF. Chest x-ray & USG A+P findings was within normal limit. Electro-encephalogram shows generalized epileptiform activity.
- USG orbit suggestive of calcific foci & cystic areas & internal vascularity within left eye likely of retinoblastoma. Left eye orbit appears smaller in size. There is no obvious extraconal extension however suboptimal evaluation due to irritable child. So, MRI orbit was advised.
- MRI Brain +Orbit reveals retinal astrocytic hamartoma with optic nerve atrophy in left eye, dysplastic cerebellar gangliocytoma in left cerebellar hemisphere, multiple variable sized subependymal nodules along bilateral ventricles & multiple cortical tubers.



T1W AXIAL T2W AXIAL T2 FLAIR

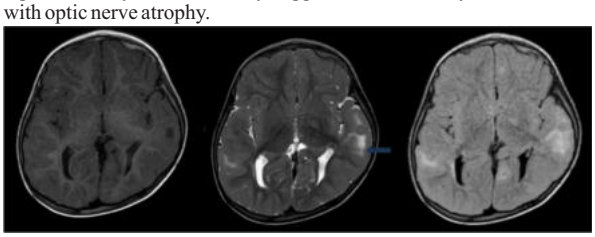


DWI ADC

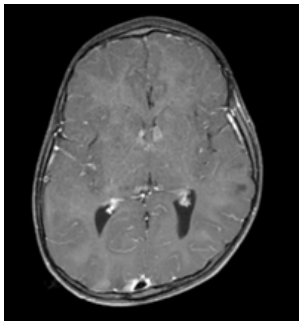


GRE Images T1 Thin contrast

Left eyeball appears small with an intraocular endophytic within appearing hypointense on T1 and isointense T2/FLAIR images and shows heterogenous post enhancement. It is showing few foci of blooming represents calcifications. No restricted diffusion. No e/o extraocular extension. Left optic nerve appears atrophic with normal signal intensity. Features likely suggests retinal astrocytic hamartoma with optic nerve atrophy.

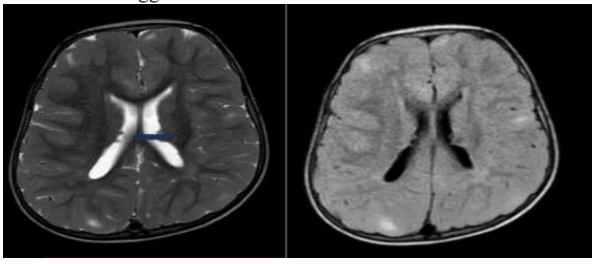


T1W AXIAL T2W AXIAL T2FLAIR

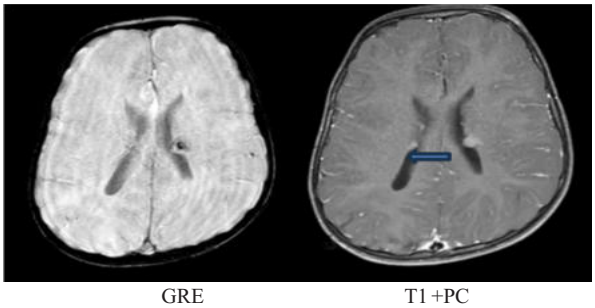


T1 POST CONTRAST

Multiple focal cortical thickening along bilateral cerebral hemisphere showing T2/FLAIR hyperintensity showing no obvious contrast enhancement suggests cortical tubers.

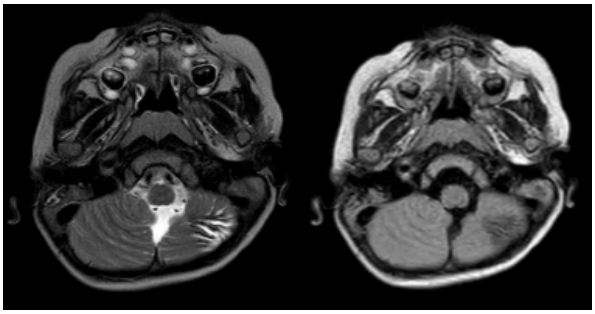


T2W AXIAL T2FLAIR

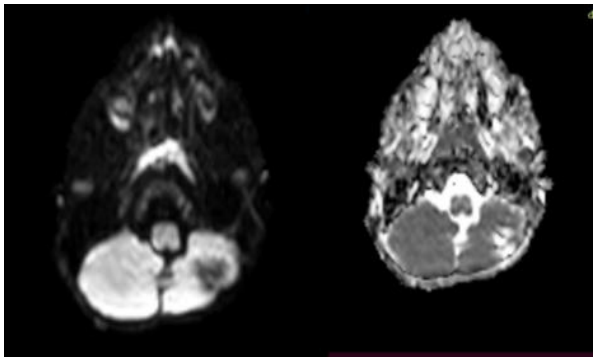


GRE T1 +PC

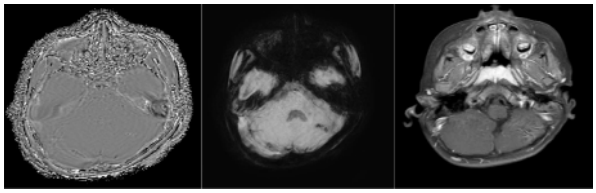
Multiple variable sized subependymal nodules along bilateral lateral ventricles appearing hypointense on T2/FLAIR images and showing subtle enhancement and blooming on GRE.



AXIAL T2 T2FLAIR



DWI ADC



GRE T1 +PC

Relatively well-defined altered signal intensity lesion measuring 1.7x1.5 cm in left cerebellar hemisphere, showing widening of cerebellar folia giving striated appearance & blooming on GRE images. It also shows subtle postcontrast enhancement.

Features likely suggests Lhermitte- Duclos disease (dysplastic cerebellar gangliocytoma)

DISCUSSION:

Tuberous sclerosis complex (TSC) is a rare neurocutaneous syndrome which variably affects the brain, kidney, heart, lungs, eyes and skin. It is characterized by neuropsychological manifestations, such as seizures, autism and cognitive disability and the formation of unusual tumour-like growths (hamartomas) in more than one organ system.[8]

TSC was first described by von Recklinghausen in 1862 and later elaborated by a French neurologist Desire-Magloire Bourneville in 1880, henceforth also known as Bourneville's disease. In 1920 Van der Hoeve first recognized retinal involvement in tuberous sclerosis. It is an autosomal dominant disorder, caused by mutations of either the TSC1 gene on chromosome 9q34 encoding hamartin or the TSC2 gene on chromosome 16p13 encoding tuberin. These two genes together form a tumour suppressor complex, which inhibit the mammalian target of rapamycin (mTOR), an evolutionarily conserved protein kinase and a major effector of cell growth.[9] The mutation in these genes leads to mTOR activation and formation of various growths and hamartomas in various organs of the body.[2,10]

The frequency of TSC is estimated to be 1/6000 to 1/10,000 live births and a prevalence of around 1/20,000.[9] TSC has clinical manifestations in different organ systems that continue to develop over the lifetime of an affected individual.[11]

The clinical features of tuberous sclerosis are highly variable, hence making the diagnosis of the disease very challenging. The classic Vogt's triad which included seizures, mental retardation, and cutaneous angiofibromas, occurs in only 29% of cases. The diagnosis is based on the TSC diagnostic criteria (recently revised in 2012) laid down by the tuberous sclerosis complex consensus group (Table 1).

About 50% of the cases with Tuberous sclerosis have ocular involvement; henceforth the role of an ophthalmologist in early diagnosis of the disease is crucial. The pathognomic retinal lesions of tuberous sclerosis are astrocytic hamartomas. They are seen in about 53% of the patients. Tuberous sclerosis typically presents with multifocal or bilateral hamartomas, as compared to solitary hamartomas occasionally present in otherwise healthy individuals. Astrocytic hamartomas can be morphologically classified into two types: (1) Large, whitish (calcified) nodular masses or (2) Flat, translucent (noncalcified) smooth tumors.[13] An intermediate type of retinal hamartoma having features of both types has also been described.[14] Rarely retinal hamartomas may be associated with

complications such as vitreous hemorrhage, retinal vascular abnormalities (including telangiectasia, neovascularization, and exudation), and vitreous seeding. Some patients may also present with astrocytomas involving the optic nerve. Optic nerve astrocytomas may initially have a greyish or greyish pink appearance, but later develop a glistening, yellow, mulberry appearance. They may cause vitreous seeding and vitreous hemorrhage. In the presence of a single retinal (or optic nerve) hamartoma, only one additional major feature, or two or more minor features, are required to make the diagnosis of tuberous sclerosis complex.

Table 1: Updated Diagnostic Criteria For Tuberous Sclerosis Complex 2012[12]

A. Genetic diagnostic criteria	The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC). A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment. Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC. Note that 10% to 25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.
B. Clinical diagnostic criteria	**Major Features** Hypomelanotic macules (≥3, at least 5-mm diameter) Angiofibromas (≥ 3) or fibrous cephalic plaque Ungual fibromas (≥ 2) Shagreen patch Multiple retinal hamartomas Cortical dysplasias Subependymal nodules Subependymal giant cell astrocytoma Cardiac rhabdomyoma Lymphangioleiomyomatosis (LAM) Angiomyolipomas (≥ 2) **Minor features** "Confetti" skin lesions Dental enamel pits (≥ 3) [5] Intraoral fibromas (≥ 2) Retinal achromic patch Multiple renal cysts Nonrenal hamartomas
Definite diagnosis	Two major features or one major feature with ≥ 2 minor features
Possible Diagnosis	Either one major feature or ≥ 2 minor features * Includes tubers and cerebral white matter radial migration lines. ** A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis

Lhermitte and Duclos reported the first case of cerebellar ganglion cell tumour in 1920. They performed a histologic examination of the lesion, finding abnormally widened cerebellar folia with abnormal ganglion cells, and labelled it diffuse ganglioneuroma. Since then, many LDD cases have been reported [15]. There is considerable controversy over the cause of this disease: it may have a hamartomatous, neoplastic, or congenital mal-formative origin [16,17].

The condition is often associated with different types of malformation such macrocephaly, megacephaly, syringomyelia, polydactyly, multiple haemangiomas and mucocutaneous lesions as well as breast, thyroid, genitourinary and gastrointestinal malignancies [18]. This has suggested a genetic correlation between LDD and Cowden's syndrome, an autosomal dominant syndrome characterised by a genetic aberration [15,16].

Imaging plays an important role in the diagnostic process. The dysplastic gangliocytoma is hypoattenuated on unenhanced computed tomographic (CT) images (Figure 1): in such cases, the only diagnostic clue may be the mass effect, which manifests as compression of the fourth ventricle, effacement of the cerebellopontine angle cistern and hydrocephalus. No appreciable enhancement is seen on contrast-enhanced CT images. However, CT remains of limited value because of the beam-hardening artifacts caused by the petrous temporal bone that obscure the details.

Conventional MRI, associated with diffusion imaging and spectroscopy, is currently the most useful imaging method able to provide a definite diagnosis by showing an expansile lesion that is typically hypointense on T1- and hyperintense on T2-weighted sequences[19]. These signal alterations are related to white matter atrophy, thickening of the granule cell layer and enlargement of the cell layers making up the cerebellar cortex. The mass is characterized by parallel hyperintense striations related to thickening of the cerebellar folia due to enlargement of the cortical cells and dysplasia of the sulci, which are considered pathognomonic signs of LDD [1]. A "tiger-striped" cerebellar lesion with unilateral hemispheric expansion and preservation of the gyral pattern [20] is reported as a specific sign for LDD and these findings often establish the operative di . Diffusion MR shows a hyperintense area at the level of the lesion, due to the "residual T2-contrast". In the apparent diffusion coefficient map, the mass appears isointense to the cerebellar parenchyma since the percentage of free water does not vary. T2 hyperintensity is due to morphological alterations of the cells making up the internal molecular layer and granular cell layer, associated with atrophy of the cerebellar white matter, thus confirming the dysplastic and malformative origin of LDD [21,22]

CONCLUSION:

Tuberous sclerosis is a rare genetic multisystem disorder that persists throughout the life. It sometimes presents with such mild symptoms that the patient is not diagnosed until adulthood. Sometimes, patients present with severe complications such as cardiac rhabdomyomas and pulmonary manifestations, which can consequently lead to death. Hence, early diagnosis and prompt treatment are necessary to prevent life-threatening com plications so that the quality of life of patients can be improved. The first step for the ophthalmologist should be, to carefully re-examine both eyes for signs of one or more retinal or optic nerve hamartomas. Our case confirms the widely accepted view that MRI, with diffusion imaging and spectroscopy are the most useful techniques in the study of Lhermitte-Duclos disease. They are able to demonstrate pathognomonic features such as thickened cerebellar folia and the be haviour of the mass at diffusion imaging and spectroscopy. Correct recognition of the disease is also particularly important given the possible association with tuberous sclerosis and therefore the need to identify concurrent malignancies.

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