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Tuberous sclerosis complex, Clinic and pathology manifestations, Mini -review

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ABSTRACT

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome that affects almost all of the organs of the body, including the brain, heart, lungs, liver, and kidneys. Brain tumors in TSC patients include cortical tubers, subependymal nodules (SENs), and Subependymal giant cell astrocytomas (SEGAs). Seizures that occur in 92% of patients with TSC are an important cause of sudden deaths in them. Other organ involvement includes renal angiomyolipomas, lymphangioleiomyomatosis, cardiac rhabdomyomas, and cutaneous manifestations (hypomelanotic macules, angiofibroma, ungual fibromas, shagreen patch, and 'confetti' skin lesions). There is a criterion for tuberous sclerosis complex that consists of 11 major and 6 minor clinical features that diagnosis occurs based on it. The best way for a definitive diagnosis of TSC in a patient is by using genetic tests and histopathology. Immunohistochemistry is a helpful method in confirming the diagnosis of brain tumors in TSC. Immunostaining of SEGA shows positivity for GFAP and S-100 protein while neurofilament and synaptophysin are negative. Ki-67, which indicates nuclear proliferation, has a low proliferation index in immunostain. In an aggressive tumor, hydrocephalus, rising intracranial pressure and focal neurologic deficit, surgery is a necessity and can improve outcomes. Brain and kidney involvement in this disease is life-threatening. Brain involvement in these patients can lead to extensive neuropsychological complications, so the aim of this study is a concise review of the variable manifestations of this disease with a focus on the histopathological findings of brain involvement.

Keywords: Tuberous sclerosis complex, Clinic, Pathology, Mini review

INTRODUCTION:

Definition of tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome that affects almost all of the organs of the body, including the brain, heart, lungs, liver, and kidneys, by developing tumors (that are developing by mutations). Biosynthesis and cell growth are controlled by two genes mutation (TSC1 and TSC2 mutation, encoding hamartin and tuberin) are responsible for inhibiting the mammalian target of rapamycin (mTOR) pathway-related up proliferation (1-4).

TSC incidence is estimated as 1 in 6000 to 10000 live births and its prevalence is estimated as 1 in 20000 in humanity (5, 6).

Associations

Primary brain tumors that arise in the parenchyma, are gliomas that histologically include diffuse and circumscribed astrocytomas, oligodendrogliomas, and ependymomas (7). Brain tumors in TSC patients include cortical tubers, subependymal nodules (SENs), and Subependymal giant cell astrocytomas (SEGAs) (1).

Other organ involvement includes renal angiomyolipomas, lymphangioleiomyomatosis, cardiac rhabdomyoma, and cutaneous manifestations (hypomelanotic macules, angiofibromas, ungual fibroma, shagreen patch, and 'confetti' skin lesions) (8, 9).

Subependymal giant cell astrocytoma (SEGA) is a category of tumors with molecular pathologic features that clinically affect children and adolescence (1, 10). SEGA is a rare benign tumor that involves the lateral ventricle and foramen of Monro, causes increasing intracranial pressure (in 5-14% of TSC patients), mental retardation (50-80% of neurological presentations), and epilepsy (more than 80% of neurological presentations) (1, 11-14).

One of the most common causes of adolescent death with tumors is brain tumors (11). SEGA is a World Health Organization grade I glioma (11, 15, 16). Seizures that occur in 92% of patients with TSC are an important cause of sudden deaths in them (17). The most reasons for mortality in TSC are neurological and renal involvements (17).

Renal involvements include angiomyolipomas (AMLs), simple cysts, polycystic kidney disease, and renal cell carcinoma (17, 18).

Cutaneous complications in TSC patients are included hypomelanotic macules, facial angiofibroma, forehead plaques, shagreen patches, and ungual fibromas (17).

The most common diagnostic features for TSC are hypomelanotic macules (94%), tubers (94%), subependymal nodules (90%), and cardiac rhabdomyoma (82%) (19).

Major and minor criteria

There is a criterion for tuberous sclerosis complex that was updated in 2012. It consists of 11 major and 6 minor clinical features that diagnosis occurs based on it (20) (Table 1).

The best way for a definitive diagnosis of TSC in a patient is by using genetic tests and histopathology (21). Although SEGA is an indicator for the diagnosis of TSC, in

Table 1. Diagnosis criteria for tuberous sclerosis complex 2012. Reprinted from reference (20)

A.Genetic diagnostic criteria
Identification of either TSC1 or TSC2 pathogenic mutation is sufficient to make a definitive diagnosis of TSC
B. Clinical diagnostic criteria
Major features:
1. Hypomelanotic macules (≥3, at least 5 mm diameter)
2. Angiofibroma (≥3) or fibrous cephalic plaque
3. Ungual fibromas (≥2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasia
7. Subependymal nodules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma
10. Lymphangioleiomyomatosis
11. Angiomyolipomas (≥2)
Minor features:
1. "Confetti" skin lesions
2. Dental enamel pits (>3)
3. Intraoral fibromas (≥2)
4. Retinal achromic patch
5. Multiple renal cysts
6. 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.

some cases SEGA has been in those whose TSC genetic test was negative or had no clinical symptoms (15, 22-24).

Skin manifestations

Seven manifestations of this criteria are cutaneous features: 4 major (hypomelanotic macules, angiofibromas or fibrous cephalic plaques, ungual fibromas, shagreen patches) and 3 minor (confetti skin lesions, dental enamel pits, intraoral fibromas).

Angiofibromas (AF) are papular red-brown skin lesions that are more prevalent in children older than 9-year-old and usually are seen in 3-year-olds and located in the central region of the face (25, 26). Along with age rising, the number of AF lesions increases (20, 26). The first shape of the lesions is vascular macules and then they become fibrotic and bumping, with dome-shaped smooth papules (27). Protection of skin from sun exposure can decrease the lesions' number progression and intensity of them (28).

Of the patients with TSC, 90% in the first year of life suffer from hypomelanosis lesions of at least 3 and more than 5 mm in size called hypomelanotic macules (ash-leaf spots), and if these lesions are smaller in size and larger in number, they are called "confetti" skin lesions (20, 29-31). Angiofibromas of the face are sebaceous adenomas that occur in 75% of cases at the age of 2 to 5 years and with increasing age and adolescence, the size and number of these lesions increase, and their shape changes. If they are bilateral with a butterfly pattern, are made of connective tissues and blood vessels that involve the central part of the face, cheeks, nasolabial folds, and chin (20, 26, 29, 32, 33).

Neurological manifestations

Subependymal lesions in the brain are of two types: subependymal nodules (SENs) and subependymal giant cell tumors (SGCTs) (34). In SGCT, the neoplastic cells proliferate from pre-existing SEN near the foramen of Monro; in other words, tumors and nodules are mass lesions in the brain that tumor cells despite nodules can proliferate and become bigger and develop symptoms in patients (34, 35). Both SEN and SGCT are mixed glioneuronal lineage and SGCT is astrocytoma and named SEGA (36, 37).

SEGA growth unlike SEN and may be larger than 1 cm in size and have a uniform spread, in terms of position, the SEN is located in the lateral ventricle in the direction of the caudate nuclei, while the SEGA is usually located in the caudothalamic groove (38). Cortical tubers have a fixed size in adults and are growing in children according to their cortical size (39, 40).

Increasing intracranial pressure (ICP) and intratumoral hemorrhage due to SEGA can cause mortality or deterioration in individuals with TSC (35). When acutely Monro foramen becomes closed, signs and symptoms of rising ICP like headache, nausea, vomiting, vertigo, and loss of consciousness in the patient become observable. If SEGA is invasive to other parts of the brain, changes in acting, focal neurologic signs, and refractory seizures become appear (41).

The risk of seizures is higher in those who have mutations in the TSC2 gene than in those who have mutations in the TSC1 gene, and even the risk of infantile spasms is higher in those with TSC2 gene mutation (42-44).

Seizure is associated with mental retardation (MR) in children (45). Patients with infantile spasms will develop more complex types of seizures in the future, although some patients develop generalized seizures from the beginning. Seizure is so common in people with TSC that 80% of children have a seizure by the age of 3 and 12% of adults without a history of seizures in adulthood. MR and refractory seizures are complications seen in these patients (44). The age of onset of a seizure is associated with mental retardation, regardless of the type of seizure, so the severity of mental retardation is greater in cases where the seizure occurred in the first three years of life (44, 46).

Mental retardation is more related to a mutation in the TSC1 gene (47). Despite the difficulty in controlling seizures, one-third of all patients and 20% of refractory cases recovered (44). Drugs that are used to control seizures in primary times and inhibit the appearance of MR are anticonvulsants. Another drug that can resolve irregularity in EEG in patients with multifocal epilepsy and

inhibit becoming MR is Vigabatrin (48-50). Other treatments are dietary therapy like low-glycemic-index dietary treatment, vagus nerve stimulation (VNS), and epilepsy surgery that can use in refractory seizures in TSC patients (44, 51). To stop the drug, it is necessary to have at least one year without clinical seizures or elimination of abnormalities in the EEG (44).

It is speculated that areas of the cortical tubers that are cyst-like may be the site of seizures or cause seizures by stimulating normal neurons. In addition to antiepileptic drugs, mTOR pathway modulators are used to control seizures (51).

SGCTs may have no symptoms and no evidence in brain CT or MRI but whereas rising intracranial pressure due to SGCT probably occurs, an ophthalmologic assessment should be done (34). A population-based study has reported that retinal hamartomas have been found in 44% of the population with TSC (45). Retinal hamartoma is most commonly seen in patients with TSC and is histologically similar to cerebral tubers but does not cause vision problems, although it is a good finding in children who may have no symptoms (20).

Another type of ocular involvement seen in TSC patients is the retinal achromic patch, which is in the form of hypopigmented areas in the retina and is seen in 39% of patients with an incidence of 1 in 20000 in the general population (20).

Genetic analyses and the use of neurological methods are used to examine the brain of these patients (video-EEG and Brain MRI). The follow-up of different patients is different based on their age and clinical indications (52). The range of neuropsychological conflicts of this disease is wide and includes seizures, mental disabilities, autism, behavioral and learning and language disorders, and other mental symptoms (52, 53).

Since seizures are lifelong and because there is drug resistance (twice the normal population) for seizures in adults with TSC (52), the rate of seizure freedom following epilepsy surgery (in the form of tuberectomy, lobectomy and multilobar resect) is reported to be 65-75%. In addition to seizure freedom, early surgery also prevents the occurrence of neurocognitive complications caused by seizures (54).

In cases such as SEGA, which leads to the occurrence of hydrocephalus and increased ICP and focal neurological deficits, surgery is necessary and prevents death (41, 55, 56). In cases where the patient is asymptomatic, a control MRI is used and the patient is serially checked for the size of the ventricle and the growth rate of SEGA. CT scan with contrast is also used to check calcification. Also, a control MRI is used to examine the remaining mass after mass removal surgery (1).

Cardiac manifestations

Involvement of a tumor of the heart, called rhabdomyoma, has a prevalence of 50% in people with TSC and 80% in children with a history of TSC symptoms in themselves or their family. The tumor is diagnosed by echocardiography and confirmed by MRI or histopathological evaluation. The number of tumor lesions also helps in the diagnosis so multiple lesions are more common in TSC patients (57). Cardiac rhabdomyoma can be asymptomatic or can cause valvular disorders, heart failure, and arrhythmias (58).

Pulmonary manifestations

Lymphangiomyomatosis is a lung disease that is normally seen in females and has a prevalence of 7 to 9 million in the female population and is commonly seen in adults with TSC. The disease manifests itself in the form of pulmonary cysts, pneumothorax, and dyspnea, which can also cause lymphatic involvement and, if progressive, lead to respiratory failure and death (59).

Renal manifestations

Angiomyolipomas are benign tumors that occurs in the kidneys and other organs of the body and are mainly made of blood vessels, smooth muscle, and adipose tissue and are seen in 80% of TSC patients. Angiomyolipoma may be fat-free and occurs in less than 0.1% of the population (20). Another renal disorder is polycystic kidney disease (PKD) which is seen along with deletion in TSC2/PKD1 genes or mutation of TSC1 or TSC2 genes (20, 45).

Histopathology and immunohistochemistry tips

In the cortical and white matter regions of tubers in TSC patients, giant cells have a cell body several times larger than normal neurons, which is due to genetic changes that have occurred in these patients (60). In the cortex and white matter of the brain in tuberal regions without SEGA-like pathology, there are large cells with abundant eosinophilic cytoplasm and ganglion-like nuclei with diffuse distribution so that the cortical areas involved with the tubers have vesicular nuclei. SEGA-like pathology in the cortex of the tuber has a large volume of neoplastic eosinophilic giant cells with glassy cytoplasm and ganglion-like nuclei dispersed by fibrillar cellular elements (3).

Numerous immunohistochemical methods are used to differentiate cells, like GFAP (glial fibrillary acidic protein) immunostain which is patched in giant cells, while it is concentrated in fibrillar elements. Despite neurofilament and synaptophysin, fibrillated spindle cells have a positive reaction to GFAP and S-100 protein (15). Ki-67, which indicates nuclear proliferation, has been reported to have a low proliferation index in MIB-1, or nothing has been identified in immunostain (3).

Conclusion

Tuberous sclerosis complex is a genetic disorder with multi-organ involvement and variable presentation. Full awareness of the clinician and pathologist of the criteria is helpful for accurate diagnosis and better management of the patient.

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Conflict of interest

None

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