Abstract. Tuberous sclerosis is a rare genetic disorder, often diagnosed based on clinical manifestations. We report a case of a 39-year-old woman retrospectively diagnosed with tuberous sclerosis after giving birth to a child with cardiac rhabdomyomas. This case highlights the awareness of clinical manifestations of orphan diseases among physicians and the need for a broader approach to managing patients, extending beyond the limited perspective of medical professionals specializing in a particular area of health and facilitated through multidisciplinary consultations, highlighting the significance of educational initiatives among specialists and the general population for early detection and implementation of corrective measures in rare genetic disorders.

Keywords: Tuberous Sclerosis; Facial Angiofibromas; Renal Angiolipomas; Cardiac Rhabdomyomas

Introduction
Tuberous sclerosis, also known as Bourneville-Pringle disease, is a rare genetic multisystem disorder, often referred to as tuberous sclerosis complex [2]. Classified as a phakomatosis (from the Greek word 'phakos' meaning spot, nevus, birth mark), it follows an autosomal dominant pattern of inheritance, with high penetrance and expressivity. In most (80%) cases, the condition results from de novo mutations [10].

The condition was first described by Friedrich Daniel von Recklinghausen in 1862. In 1880, French physician Desire-Magloire Bourneville conducted a comprehensive examination of a female patient affected with tuberous sclerosis, while British dermatologist John James Pringle provided a description of benign tumors found on the patients’ faces. The estimated incidence of tuberous sclerosis is one in 6,000-10,000 newborns, while in adults, its incidence rate ranges between 1 in 20,000 and 1 in 100,000 individuals [4]. Males and females are affected with equal frequency.

Tuberous sclerosis is caused by the mutation of tumor suppressor genes, TSC1 or TSC2, located on 9q34 and 16p13.3, respectively [11,12]. These genes encode the hamartin and tuberin proteins, which act as natural tumor growth suppressors. The proteins inhibit mTOR kinase, which is involved in regulating cell proliferation and migration [7]. The type and distribution of nearly 1,000 mutations within these two genes are discussed. Mosaicism for tuberous sclerosis has been documented, which presents challenges in providing genetic counseling to families. Established genotype-phenotype correlations have enhanced treatment outcomes [5].

Bourneville-Pringle disease is diagnosed based on syndromic management approach, clinical genealogical analysis, paraclinical examinations, and molecular genetic testing. In 2012, the main diagnostic criteria and recommendations for managing patients with tuberous sclerosis were revised and updated in the second International Tuberous Sclerosis Complex Consensus Conference held in Washington [8].

The condition has a broad spectrum of clinical manifestations, which can be classified into four groups, including classic, neuropsychological, cutaneous, and cerebrosal features. The major and minor diagnostic criteria for tuberous sclerosis have been established. For the definitive diagnosis of Bourneville-Pringle disease, either two major features, or one major feature and two minor features are required. Other cases require further examination [1].

Major features of tuberous sclerosis include:
- facial angiofibromas (three or more) or fibrous cephalic plaques;
- hypomelanotic macules (three or more, at least 5 mm in diameter);
- shagreen patch;
- multiple retinal hamartomas;
- cortical dysplasia, tubers, and cerebral white matter migration lines;
- subependymal nodes;
- subependymal giant cell astrocytoma;
- cardiac rhabdomyoma;
- lymphangioleiomyomatosis;
- multiple angiofibromas (two and more);
- non-traumatic periungual fibroma (two and more).

Minor features of tuberous sclerosis include:
- ‘confetti’ skin lesions;
- dental enamel pits (three and more);
- intraoral fibromas (two and more);
- retinal achromatic patches;
- multiple renal cysts;
- internal organ hamartomas.

According to Article 53-1, Section V of the Law of Ukraine “On Fundamentals of the Legislation of Ukraine on Healthcare”, the Ministry of Health of Ukraine approved by Order No. 778 dated October 27, 2014 (as amended by Order No. 919 of the Ministry of Health dated December 30, 2015) the list of rare (orphan) diseases that diminish patients’ life expectancy or cause disability and for which recognized treatment methods exist, including tuberous sclerosis. International Tuberous Sclerosis Awareness Day, which falls on May 15, is aimed at raising awareness of tuberous sclerosis and other rare diseases given in the list.

Despite the considerable attention this disease receives...
in society and the advancements in diagnostics and treatment, it often remains underdiagnosed. That is because tuberous sclerosis is characterized by pronounced clinical polymorphism and genetic heterogeneity, requiring multisystem consultative support and specific examinations. Reporting cases of this rare condition, in our opinion, would be highly beneficial for improving the professional competence of physicians across various specialties (especially dermatologists, neurologists, ophthalmologists, nephrologists, internists, and geneticists).

The authors obtained consent from the patient for publishing the article and photos.

**Case Report**

A 39-year-old woman with complaints of multiple facial nodules, frequent headaches, dizziness, short-term numbness, back pain, and fatigue was referred to genetic counseling by a neurologist.

Based on the clinical and genetic history, it was found that similar facial nodules were present in the proband’s father, who died at the age of 73 years, and paternal grandmother. Proband’s relatives did not seek medical assistance. Among the patient’s four children, three boys exhibited no evident signs of the condition. However, the fourth child, a girl, was born with a congenital heart defect - multiple rhabdomyomas in both ventricular cavities. Further examination of the girl revealed multiple cortical tubers. Considering the child’s symptoms, the mother was suspected to have tuberous sclerosis.

The patient had no outpatient medical record. According to her medical history, she has been affected by the condition since childhood, which consequently led to academic challenges during schooling. Due to cognitive impairments, the patient paid no attention to symptoms for a long period of time. The patient reported that the first cutaneous manifestations developed at the age of four and they were interpreted as acne. She consulted a dermatologist; however, there are no records in her medical history. Around the age of ten, periungual fibromas began to appear, accompanied by deformation of the nail plates. In 2018, the patient received treatment for right-sided paranephritis. As documented in the inpatient discharge summaries, the patient underwent surgery involving drainage of the paranephric region, followed by the first performance of computed tomography (CT) of the abdominal cavity. Right-sided paranephritis was detected, prompting suspicion of von Hippel-Lindau syndrome. In 2020, the patient underwent treatment for monofocal renal angiomyolipoma. In 2022, due to worsening headaches and dizziness, she consulted a neurologist and a geneticist.

The laboratory values obtained were within normal ranges. The CT scan showed multiple angiolipomas in both kidneys, sclerotic lesions throughout the skeleton, hepatosplenomegaly, and cholelithiasis. Magnetic resonance imaging (MRI) of the brain revealed multiple subcortical tubers in the two cerebral hemispheres and the right cerebellar hemisphere. The electroencephalogram showed diffuse changes with no electrical activity in the cerebral cortex.

The physical examination uncovered multiple angiofibromas involving the nose, chin, and nasolabial folds. These were multiple, sometimes confluent, oval, or round papules of a firm texture, measuring between 1 to 5 mm in diameter, with well-defined boundaries and a smooth surface. The papules were the same color as the normal surrounding skin (Fig. 1.1, 1.2). Depigmented patches of skin were identified on the trunk and extremities (Fig. 2). In addition, periungual fibromas, or Koenen tumors, measuring up to 3 mm were noted on the upper and lower extremities (Fig. 3). Oral cavity examination revealed gingival hyperplasia and fibromas (Fig. 4) and tongue lesions.

Fig. 1.1. Angiofibromas in the nasolabial folds, on the nose and chin

Fig. 1.2. Close-up showing angiofibromas on the nose and chin
Results and Discussion

Tuberous sclerosis is a rare genetic disorder characterized by multiple manifestations in many body organs and systems. The prognosis depends on the severity of clinical signs. In severe cases, death may occur in childhood due to epilepsy, heart, or kidney failure. However, the condition may present with mild signs and symptoms. In such cases, a detailed syndromic evaluation of all body organs and systems is crucial.

The most common manifestations of tuberous sclerosis are skin changes presenting as sebaceous adenomas on the face, known as angiofibromas [9]. These angiofibromas typically emerge at the age of 4 and are prevalent in 47% to 90% of cases [12]. They manifest as small, pink-to-red nodules situated in the nasolabial folds, on the chin and cheeks, displaying a distinct butterfly-like pattern. Our patient first noticed them during childhood (Fig. 1.1, 1.2). Nevertheless, both inappropriate attitude towards the child’s health and underestimation of diagnostic signs by physicians impeded the suspicion of Bourneville-Pringle disease.

Other signs of the disease are connective tissue naevi, known as shagreen patches, which are small, thickened fibrous plaques that feel rough on palpation [2]. Typically arising around the age of 20, they are primarily localized in the lumbosacral region and can range in size from 1 to 10 cm. The examination of our proband revealed no connective tissue changes on the skin.

Periungual fibromas, or Koenen tumors, manifest as dark fibrous growths around and beneath the nails, with a higher prevalence on the toes than on the fingers. They range in size from small to 10 mm, typically emerge after puberty, and are more frequent in women [2]. These features were verified in our patient, on both lower and upper extremities (Fig. 3).

In 90% of cases, 3-4 to 100 asymmetric hypopigmented (light) patches are observed [6]. They are either present at birth or develop within the first three years of life, with a tendency to increase in size over time. In tuberous sclerosis, hypopigmented patches are predominantly found on the trunk and buttocks. ‘Confetti’ skin lesions are numerous 1- to 3-mm hypopigmented macules scattered over the extremities (Fig. 2).

Consistent with the majority of patients, our case also presented with multiple fibromas within the oral cavity (more than two) (Fig. 4) [2].

Multiple renal hamartomas and achromic patches are ophthalmologic features of Bourneville-Pringle disease. Renal hamartomas are histologically similar to central nervous system (CNS) tumor in tuberous sclerosis. These renal lesions do not affect vision and are reliable markers for the disease.

The clinical involvement of the CNS presents as varying degrees of intellectual disability, epileptic seizures, behavioral disturbances, and sleep-wake cycle alterations. Seizures, detected in 80-92% of cases, frequently stand out as a prominent symptom of the condition. They may manifest as either West syndrome (infantile spasms) or Lennox-Gastaut syndrome (a variant of myoclonic atonic epilepsy); however, they more frequently appear as somatomotor attacks or secondary generalized seizures.
In tuberous sclerosis, epileptic seizures are often resistant to conventional therapy. Intellectual disability is often accompanied by behavioral changes, including autism, hyperactivity, and aggressiveness [3].

Cortical tubers, subependymal nodules, and white matter abnormalities are the most common brain lesions seen in tuberous sclerosis. The localization, consistency, shape, and size of cortical tubers vary. Calcification in cortical tubers occurs in 54% of cases, and its incidence increases with age. The best imaging modality for verifying tubers during patient examination is MRI, which enables their visualization in 95% of cases. Subependymal nodules are present in 95% of cases and are identifiable on both CT and MRI brain scans.

Rhabdomyomas develop in 30-60% of cases, with a male predominance (gender ratio 2:1). Newborns (21 out of 23) and infants (11 out of 33) with tuberous sclerosis are more likely to have cardiac rhabdomyomas [14]. Tumors can manifest as either singular or multiple nodules. Cardiac rhabdomyomas are rarely found in the atria, originating from the interatrial septum. They can be detected prenatally with the use of sonography as early as the 21st week of gestation. In all cases of prenatal tumor diagnosis in a newborn, tuberous sclerosis should be excluded, even in the absence of a family history [5].

The respiratory organs are involved in 1% of patients with tuberous sclerosis, with a higher prevalence among women. According to various sources, the kidneys are involved in 47-85% of cases [2]. Angiomyolipomas are observed in 48% of patients, cysts in 35%, and a coexistence of angiomyolipomas and cysts is found in 17% of patients. Other tumor types, including renal cell carcinoma (5%), oncocyotma, and focal segmental glomerulosclerosis are rarely seen.

This case is unique due to late diagnosing the condition, at the age of 39 years, despite the presence of specific clinical signs and symptoms, a three-generation family history, and periodic observations by various specialists. Additionally, the diagnosis was made retrospectively after the birth of a child with cardiac rhabdomyoma. This suggests the lack of awareness concerning orphan diseases, poor interdisciplinary collaboration among medical professionals, and a relatively low level of medical community awareness of this pathology. The delayed diagnosis can also be attributed to the fact that affected family members - the proband’s father and grandmother, presented with minimal symptoms, lived an average lifespan, and did not seek medical care. As a results, skin manifestations were perceived by the patient as minor family traits. An early diagnosis of the disease, however, could have improved the effectiveness of the patient’s and her child’s treatment, delaying, or preventing the onset of severe complications.

Conclusions

Tuberous sclerosis is a rare genetic disorder characterized by multiple organ involvement with development of multiple benign tumors that gradually impair organ function. Timely diagnosis and quality monitoring prevent complications and help the patient become a functional member of society. A multidisciplinary approach, including genetic counseling, is the primary direction for managing patients with tuberous sclerosis.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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References

12. Consortium ECTS. Identification and character-
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