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REVIEW

Phacomatosis

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ABSTRACT

Neurocutaneous syndromes are a group of genetically transmitted diseases with skin lesions, of which more than 60 types have been defined and are of ectodermal origin. Except for ataxia-telangiectasia, all are autosomal dominant. These syndromes are significant in neuro-oncology because they create a predisposition to cancer and cause the formation of a wide range of tumors, from hamartomas to malignant tumors. There is no curative treatment in these syndromes; their treatments are symptomatic and surgical treatment is preferred only due to severe neurological deficits and increased mass effect. This article aims to re-summarize the clinical features of common neurocutaneous syndromes in light of current developments.

Keywords: Phakomatosis. Neurofibromatosis. Optic glioma. Von hippel-lindau. Tuberosklerosis.

Fakomatozlar

ÖZET

Nörokütanöz sendromlar ektodermal kökenli 60'ın üzerinde tipi tanımlanmış olan cilt bulguları ile bulunan genetik geçişli bir grup hastalıktır. Ataksi-telenjiektazi hariç hepsi otozomal dominant geçişlidir. Bu sendromlar kanser yatkınlığı oluşturdukları ve hamartomlardan malign tümörlere uzanan geniş bir yelpazede tümörlerin oluşumuna neden oldukları için nöroonkolojide son derece önemlidirler. Bu sendromlarda küratif tedavi bulunmamaktadır, tedavileri semptomatiktir ve cerrahi tedavi ancak ciddi nörolojik defisit ve artmış kitle etkisi sebebi ile tercih edilmektedir. Bu yazının amacı sık görülen nörokütanöz sendromların klinik özelliklerini güncel gelişmeler ışığında yeniden özetlemektir.

Anahtar Kelimeler: Fakomatozlar. Nörofibromatozis. Optik gliom. Von hippel-lindau. Tuberoskleroz.

First introduced by an ophthalmologist named Van Der Hoeve in the early 20th century, phakomatoses were initially divided into three categories: Neurofibromatosis, Tuberous Sclerosis Complex, and Von Hippel-Lindau Disease. The term "phakomatoses," derived from the Greek word meaning "birthmark," refers to hereditary conditions that predominantly follow an autosomal dominant genetic inheritance pattern, with some exceptions[1]. These disorders affect ectodermal tissues such as the skin, eyes, and nervous system. To date, 67 types of phakomatoses have been identified[2]. Phakomatoses are considered highly significant in neuro-oncology due to their predisposition to cancer and tumor formation. In the latest classification by Ruggieri and his team in 2020, phakomatoses were grouped into six main categories: Neurofibromatosis types 1 and 2 (NF), Tuberous Sclerosis (TS), Sturge-Weber Disease (SW), Von Hippel-Lindau Disease (vHL), and Ataxia-Telangiectasia (AT)[2].

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Material and Method

We conducted a review of published literature in Turkidh Turkish and English. Ovid Medline, Ovid Embase, CINAHL, and Web of Science were searched for the terms "Neurofibromatosis 1", "Neurofibromatosis 2", "Von Recklinghausen", "Tuberous Sclerosis", "Sturge-Weber Disease", "Von Hippel-Lindau Disease", "Ataxia-Telangiectasia". We included articles that were peer-reviewed in primary studies, reviews, or meta-analyses. We excluded studies with only participants without phacomatosis, case reports, and case studies.

Neurofibromatosis

The term neurofibromatosis first entered the medical literature in 1882, when Friedrich von Recklinghausen coined it from "neurofibroma"[3].

Neurofibromatoses were initially considered a single disorder. Initially considered a single disorder, neurofibromatoses now have eight recognized types in the literature, with NF Type 1 and NF Type 2 being the most common. The term "neurofibromatosis" comes from the Latin for "nerve fibroma." These conditions lead to the formation of tumors along the nerve pathways, including in the brain, spinal cord, and peripheral nerves. Additionally, neurofibromatoses account for about 0.6% of pediatric cancers, specifically related to NF1. They are observed in about 1 in 3,000 people, regardless of gender or race[4].

Neurofibromatoses manifest in two forms: mosaic and segmental[4]. If the mutation occurs after fertilization, the pathogenic variant is present in some cells, meaning the signs of NF are not confined to specific areas; this is known as mosaic neurofibromatosis[3]. In segmental neurofibromatosis, however, the characteristics of NF are usually limited to a specific region.

Neurofibromatosis Type 1

Neurofibromatosis Type 1 (NF1), the most common syndrome accounting for 90% of all neurofibromatoses, is a neurocutaneous syndrome caused by a single gene. The NF1 gene is located on chromosome 17 and contains over 60 exons and more than 300 kilobases of DNA[5]. The prevalence of NF1 in the population is approximately 1-5 per 10,000, with an occurrence rate of about 1 in 3,000-4,000 births[6]. Tumors develop due to a variant in the NF1 gene, which encodes the protein neurofibromin that prevents tumor formation. This condition is observed in approximately half of the patients due to familial inheritance, while the other half arise from sporadic gene variants. In a small but significant portion of patients (about 5%), a microdeletion of the entire NF1 gene, which leads to more severe internal and external manifestations, is observed[7]. Café-au-lait macules (Figure 1), Lisch nodules, gliomas, neurofibromas, and bone dysplasias are some characteristic findings that occur due to NF1[8]. Given the 100% penetrance of the NF1 gene, it is impossible for individuals with the mutation not to display any clinical symptoms.

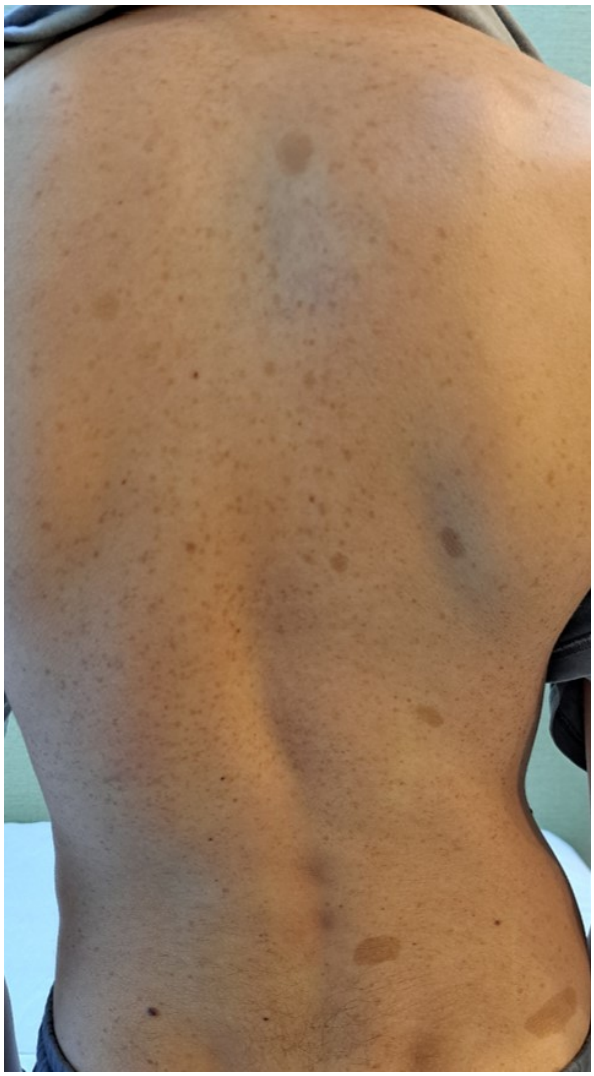

Figure 1.

Multiple café au lait spots are present at birth and increase in number and size over the years. These spots have no malignant potential. They darken in the sun and fade with age. Freckles are usually observed bilaterally (90%) in areas not exposed to the sun, such as the groin and armpits[9].

Neurofibromas can be observed in the peripheral nervous system. These can be cutaneous (85%) in the form of soft nodules on the skin or larger pedunculated and sagging subcutaneous (20%) (Figüre 2). Neurofibromas do not have malignant potential. They affect patients cosmetically. Pinti et al. reported that the probability of developing MPSKT is higher in those with at least two subcutaneous NF[10].

Plexiform NFs are more complex NFs that originate from more than one nerve fascicle or nerve plexus, involve the main nerves, extend along the main nerves, can be internal or external, and can reach giant sizes in large bundles (Figure 3).

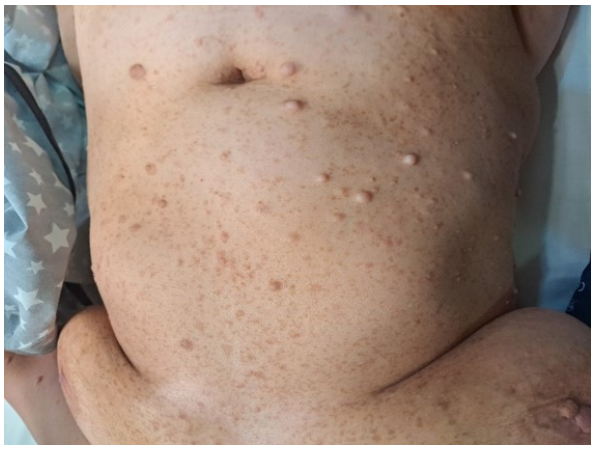

Figure 2.

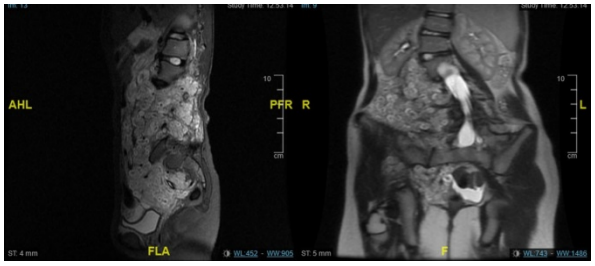

Figure 3.

The onset of pain, the increase in the size of the mass, and the development of malignant change in new neurological findings are signs of malignant transformation. The frequency of malignant peripheral nerve sheath tumor in the general population is 0.001%. 50% of all malignant peripheral nerve sheath tumor cases are NF1

Learning disability (50%), attention deficit, social interaction problems can be observed. Less than 10% of NF1 patients have intellectual disabilities, and 4-13% have epilepsy. Macrocephaly and short stature are standard phenotypic features in these patients.

In 75-90% of patients, hyperintense white matter lesions with well-defined borders called unknown brain objects (UBO) are observed on T2 MRI. These lesions are most commonly seen around the age of 7 and often disappear by puberty[2].

Optic glioma accounts for 2-5% of childhood CNS tumors, 70% of which are NF1. In routine MRI scans of children with NF1, optic glioma is detected in 15% to 20% (Figure 4). Care should also be taken in NF 1 patients in terms of diencephalic syndrome.

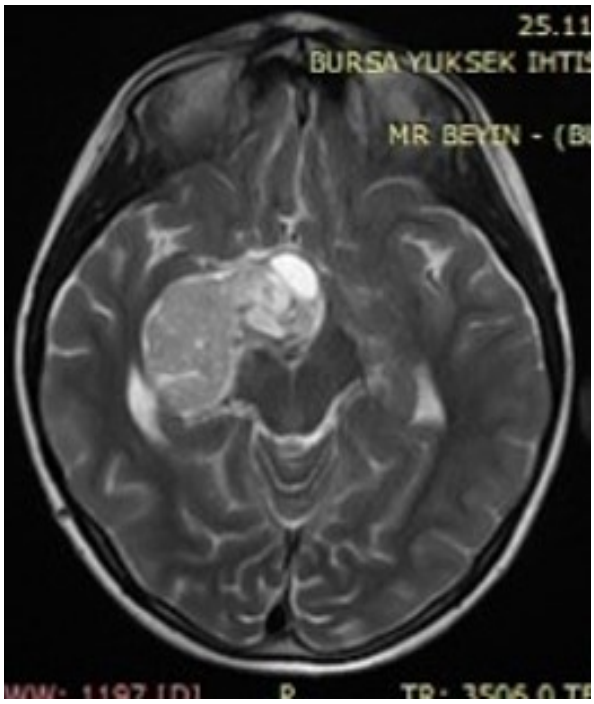

Figure 4.

The standard criteria for diagnosing NF1, established by the National Institutes of Health (NIH) in 1987, were updated in 2021, resulting in the current criteria (Table I)[3]. An NF1 diagnosis is made if two or more of the seven established criteria are present in the patient. While NF1 is known to be a hereditary disease, the criteria met, and the severity of symptoms can vary within a family. challengingGenetic testing may be conducted if diagnosing NF1 is difficult or cannot be clearly distinguished from similar syndromes. If NF1 is identified in a family for the first time, there is a high likelihood that mosaic NF1 may be present in the parents, and this possibility should be investigated. However, if neither parent shows any symptoms, the likelihood of NF1 recurring in the second generation is low.

Table I.

1	Optic glioma
2	Freckling in the ingunial or the axillary regions
3	2 or more Lisch nodules(iris hamartomas)
4	2 or more neurofibromas of any type or one plexiform neurofibroma
5	A distinctive osseous lesion (sphenoid dysplasia or thinning of long bones)
6	Sixx café au lait spots >5 mm in diameter in prepubertal children or >15 mm in postpubertal children
7	A first-degree relative with neurofibromatosis type 1

Neurofibromatosis Type 2

Neurofibromatosis Type 2 (NF2) is observed in approximately 1 in 25,000 to 40,000 individuals and has a prevalence of 1 in 56,000. It was first introduced to the medical literature in 1822 when John H. Wishort encountered it in a deaf patient[3].

NF2 is caused by a variant of the NF2 gene located on chromosome 22, which is responsible for suppressing tumor formation[5]. Like NF1, NF2 is hereditary, but it is rarer compared to NF1. NF2 has important features, such as the production of the Merlin protein, and plays an inhibitory role, particularly in mammalian cells[2]. NF2 is typically characterized by schwannomas, meningiomas, and ependymomas. These lesions usually appear bright on T2-weighted images and may sometimes present in a cystic form.

Hearing loss and tinnitus in the 20s are among the most common symptoms of Neurofibromatosis Type 2. In pediatric cases, juvenile posterior subcapsular cataract and skin tumors are key findings on the path to diagnosis. Additionally, the absence of Lisch nodules combined with the presence of bilateral vestibular schwannomas is one of the most definitive diagnostic features for NF2[3]. The phenotypes observed in individuals with functional loss are generally much more severe than those seen in individuals with large mutations. lower. NF2 is diagnosed when at least two diagnostic criteria from institutions such as the National Institutes of Health and Manchester are present in a patient (Table II)[11].

Table II.

1	A first-degree relative with NF2 AND either • Unilateral vestibular schwannoma OR • Any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
2	Unilateral vestibular schwannoma AND • Any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
3	Multiple meningiomas AND • Unilateral vestibular schwannoma OR • Any two of schwannoma, glioma, neurofibroma, cataract
4	Bilateral vestibular schwannomas

There are three types: 1. Congenital (neonatal) type with small bilateral VIIIth nerve schwannomas that progress suddenly in infancy 2. Wishart (severe) (childhood) type with multiple and rapidly progressing CNS tumors other than VS that appear at an early age and may appear years before VS, leading to multiple tumors and death in the 40s 3. Gardner (adult) type with a milder course together with meningiomas

In NF2, the Lisch nodule of NF1 is not seen, and a special type of cataract known as juvenile posterior sublenticular opacity (30-40%) develops. Cataracts under the age of 50 can be considered specific to this disease.

There is no specific lesion on the skin. 65% of patients also have cutaneous nerve sheath tumors[12]. Meningiomas are the second most common tumors in NF2 (20%). Intracranial meningiomas are often multiple, located along the falx cerebri or cerebral convexity (Figure 5). Ependymomas account for over 75% of intramedullary spinal cord tumors associated with NF2[12].

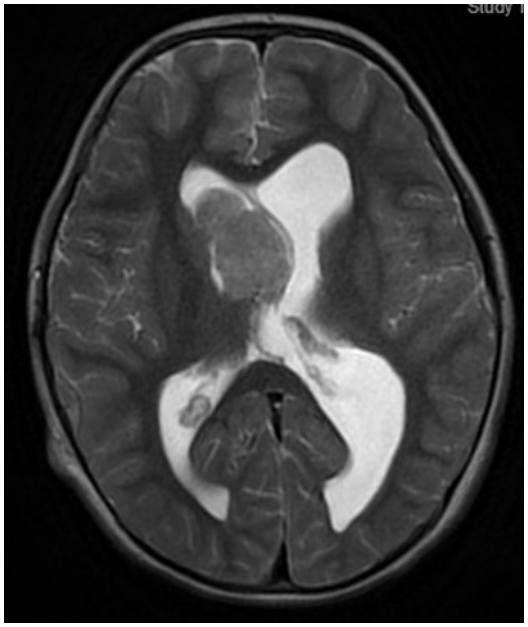

Figure 5.

NF3 Schwannomatosis

It is seen in 1/40,000 frequency. Vestibular Schwannomas and other tumors are not seen, deafness and learning difficulties do not develop. It is usually sporadic, but 10% of cases are familial and often skip generations.

Von Hippel-Lindau Disease

Von Hippel-Lindau (VHL) disease is a rare type of phakomatosis and a neurocutaneous syndrome. It was first described in the medical literature in 1904 by German ophthalmologist Eugen Von Hippel, who observed angiomas in the eye, and in 1927 by Swedish Arvid Lindau, who observed cerebellar hemangio-

blastomas. VHL is observed in approximately 1 in 36,000 births and affects around 200,000 individuals worldwide. The prevalence is 1/53,000, and it is inherited in an autosomal dominant manner[13]. The VHL gene, located on the short arm of chromosome 3 and consisting of 3 exons, has a broad mutation spectrum[5]. As a tumor suppressor gene, VHL is responsible for various tumors in the central nervous system, leading to Von Hippel-Lindau disease. Loss of function of VHL results in the formation of vascular tumors and the activation of hypoxia-inducible genes. About 80% of individuals with VHL have at least one parent with the disease, while in the remaining 20%, the disease is due to a mutation in the gene during fertilization[14]. With modern technology, prenatal detection of VHL can be performed through molecular analysis of chorionic villus cells or preimplantation genetic testing. Patients are observed to have at least one tumoral lesion within the first 65 years of life, as the penetrance of VHL reaches 100% by age 65[2].

In cases of Von Hippel-Lindau (VHL) disease, 50% of the cases involve retinal hemangioblastomas[3]. These tumors can lead to vision loss if they bleed. About 40% of cases consist of central nervous system hemangioblastomas. Although these tumors are generally benign, they can cause problems by compressing nearby nerves. This group is classified into four main categories: simple cysts without macroscopic nodules (5%), cysts with mural nodules (60%), solid tumors (26%), and solid tumors with small cysts (9%)[3].

Melmon and Rosen established the diagnostic criteria for Von Hippel-Lindau (VHL) syndrome and Rosen established the diagnostic criteria for Von Hippel-Lindau (VHL) syndrome in 1964[2]. According to these criteria, if a patient's family history is available, the presence of one hemangioblastoma or a visceral tumor is sufficient to make a diagnosis. However, if the patient's history is unknown, the diagnosis requires at least two hemangioblastomas or one hemangioblastoma along with one visceral tumor[14]. Due to the location of the tumors, surgical intervention is often necessary for treatment.

They are usually located in the posterior fossa (75% cerebellar) and craniocervical junction. 5-30% of cerebellar HB is related to VHLH. The most common (60%) is the mural nodule cystic type. If there is cerebellar HB, the spinal cord should definitely be scanned for lesions. 80% of spinal HB is related to VHLH.

Tuberous sclerosis

Tuberous sclerosis, a neurocutaneous syndrome, was first observed in 1862 by Friedrich Daniel Von Recklinghausen. However, Désiré-Magloire Bourneville identified it as a distinct syndrome, leading to it also being known as Bourneville disease[2]. Tuberous sclerosis (TS) is an autosomal dominant phakomatosis, also referred to as Epiloia, because patients experience epilepsy and developmental delays[3]. Two-thirds of cases arise from spontaneous mutations. It occurs in approximately 1 in 6,000 births, with a prevalence of 3-10 per 100,000, and about 1 million cases worldwide. There is no gender difference, although the phenotype tends to be milder in females[3].

The syndrome is caused by inactivating mutations in the TSC1 and TSC2 genes located on chromosomes 9 and 16, respectively[7]. Inherited paternal TSC1 mutations result in milder phenotypes, whereas sporadic TSC2 mutations lead to more severe phenotypes. TS can affect all organ systems, including the brain, skin, eyes, and kidneys[7]. Symptoms usually present before the age of 5 but can sometimes remain hidden until adolescence[2].

The most significant symptom is seizures, which affect more than 75% of patients and lead to cognitive impairments, behavioral problems, and learning difficulties. The disease often becomes symptomatic before the age of 5. Skin lesions are observed in 95% of patients. Ash-leaf macules (ALM) are hypopigmented macules and are usually present at birth. Adenoma sebaceum (Facial angiofibroma) is observed in 47% of cases[15].

Multiple retinal hamartomas in the eye, depigmented spots on the iris and retina, cataracts, corneal anomalies, vision loss after extensive retinal lesions, and strabismus may be observed.

The most common cause of morbidity is neurological findings. In 75-90% of patients, seizures that begin in infancy are observed. Intellectual disability is seen in less than 50% of patients. Increased cortical tuber size increases the risk of intellectual disabilities. Learning problems, behavioral disorders, autism (25%), autistic spectrum disorder (25%), focal neurological deficits, and ataxia can be seen.

More than 95% of cases have cortical tuberculosis, white matter lesions, SEN or SEGA detected on MRI.

Cortical tuber hamartoma is a cortical dysplasia that can be slightly pale, hard, flat or granular and is seen as a gyrus expansion in the convexity in 95% of cases. It is located mainly located supratentorial and rarely grows. Epilepsy severity and infantile spasms are related to the number, size and location of the KT[16].

Subependymal nodules are hamartomatous lesions located along the ependymal surface of the lateral ventricle, in the striotalamic groove between the caudate nucleus and the thalamus, just posterior to the foramen of Monro. Calcified SEN, especially seen in the vicinity of the foramen of Monro, is typical.

SEGA is often unilateral and develops in the subependymal region of the foramen of Monro (Figure 6). SEGA is at least 10 mm in diameter, SEGAs typically occur in the caudothalamic groove, while SENs occur along the ependyma in the lateral ventricle. SENs may calcify

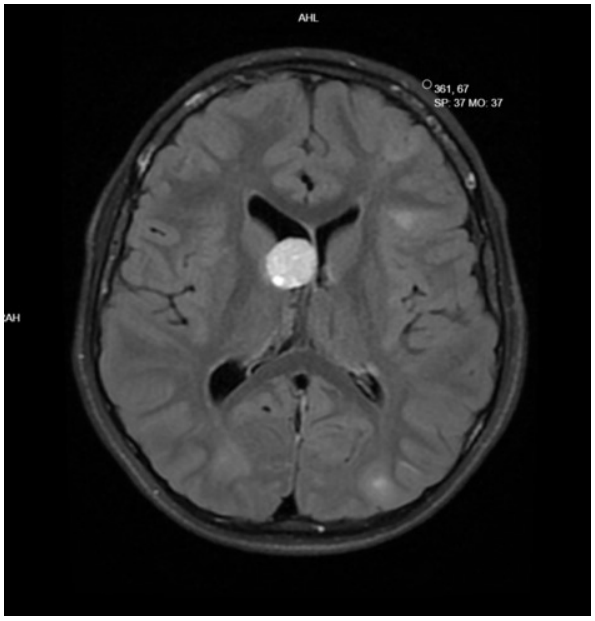

Figure 6.

Although managed with medication, surgical intervention may be needed if lesions are detected. Prenatal diagnosis is possible via MRI during the 20th to 26th weeks of gestation[2]. The International Tuberous Sclerosis Complex Consensus Group updated the clinical criteria in 2021[3].

Sturge-Weber Syndrome

Sturge-Weber syndrome is a rare phakomatosis that is not inherited, unlike similar conditions[8]. Symptoms usually start in childhood and include seizures and skin abnormalities known as "nervus flammeus" or port-wine stains, especially at the V1 dermatome (Figure 7). This syndrome often leads to seizures in 80-90% of those affected, with intellectual disabilities and hemiplegia present in 60% of cases and either of these conditions occurring in 30% of cases[2]. Treatment primarily aims to address the symptoms, using antiepileptic drugs to control seizures. In cases where medication fails to manage epilepsy effectively, lobectomy might be required.

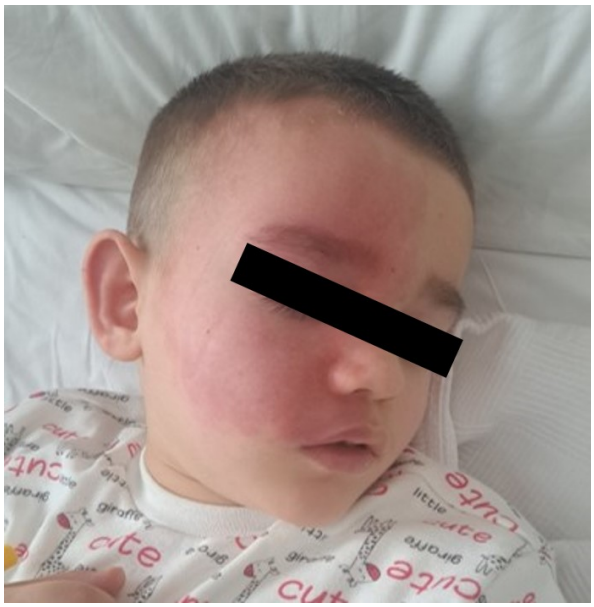

Figure 7.

Ataxia-Telangiectasia

Ataxia-telangiectasia, also known as Louis-Bar syndrome, is a rare genetic disorder that often leads to death due to recurrent infections and developing tumors. It is located on the long arm of chromosome 11 and follows an autosomal recessive inheritance pattern[2]. This condition causes ataxia, which affects coordination, balance, and walking. It also leads to telangiectasia, characterized by red spots on the skin due to dilated blood vessels. Additionally, it causes immune system problems and neurological issues. The first symptom is a delay in walking due to cerebellar ataxia. Death often occurs in the 3rd or 4th decade due to recurrent infections and the development of malignant tumors.

Conclusion

Phakomatosis is a group of hereditary syndromes that show phenotypic overlap with each other and with other genetic syndromes. The presence of characteristic cutaneous features and certain tumor types should raise the possibility of phakomatosis. The clinical manifestations of phakomatosis are highly variable, and treatment and follow-up vary for each phakomatosis patient.

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