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Research Article

CASE SERIES OF CHILDREN WITH NEURO-CUTANEOUS SYNDROMES

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Abstract

Neurocutaneous syndrome (Phakomatoses) is a genetic disorder affecting the skin and nervous system, characterized by benign tumours or malformations. It includes Tuberous Sclerosis Complex (TSC), Sturge-Weber Syndrome, Neurofibromatosis, Incontinentia Pigmrnti, Ataxia Telangiectasia etc. These disorders are inherited in autosomal dominant and autosomal recessive ways, with some being sporadic and having a genetic predisposition in rare cases. The case series aimed to examine the clinical profile of children with Neurocutaneous syndrome, their symptoms, seizure type and treatment response. This prospective observational study was conducted at Pushpagiri Medical College Hospital in Tiruvalla, India, involving 10 children with various forms of NCS between the ages of 0-15, four cases of Sturge weber syndrome (SWS), two cases of neurofibromatosis (NF-1), two cases of Hypomelanosis of Ito, one case of Tuberous sclerosis complex, and one case of Incontinentia pigmenti. Sturge Weber syndrome involved non-neoplastic congenital dermal capillary hamartomatous malformation, with neurological symptoms including generalized tonic-clonic seizures, muscle stiffness, rhythmic jerking movements, and 50% partial/ focal seizures. Neurofibromatosis type 1 is a genetic disorder in children, with two children in the study showing mild symptoms and café au lait spots. Hypomelanosis of Ito affected two children out of ten, experiencing 50% generalized tonic-clonic seizures and developmental delays. Tuberous sclerosis complex was confirmed in one child with hypomelanotic macules, focal seizure, hypopigmented streaks, and patches in a 'whorl-like' distribution typical of HI with 100% developmental delays. TSC was caused by mutations of the TSC1 gene on chromosome 9, which encodes hamartin, and the TSC2 gene on chromosome 16, which encodes tuberin. It was concluded that these syndromes have severe neurological features and developmental issues, requiring multiple therapies. NF-1 has a high prevalence of generalized seiszure. Hypomelanosis of Ito has multi-organ involvement, and the Tuberous Sclerosis complex has severe developmental impairment and dermatological manifestations. The series emphasizes the need for early detection and individual care approaches to improve children's lives.

Keywords: Neurocutaneous, Autosomal, Recessive, Genetic disease, Hypo pigmented, Case Series.

INTRODUCTION

Neurocutaneous syndrome (Phakomatoses), a group of genetic disorders, is primarily an individual's skin and nervous system. This group of diseases is distinguished by hamartomas, which are benign tumours/developmental malformations occurring in the context of composite structures and consisting of a nodule of all the tissues found in affected body areas. The term 'Neurocutaneous' implies neurological and dermatological manifestations of a disease caused by the common embryological origins of the skin and nervous tissue (Ruggieri *et al.,* 2020). Neurofibromatosis NF is classified into two main types: 1) NF1 (von Recklinghausen's disease) and 2) NF2 (bilateral acoustic neurofibromatosis). NF1 is identified by Café-au-lait spots, neurofibromas, freckling or Lisch nodules, and optic gliomas. NF2 is bilateral acoustic neuromas, meningiomas, and juvenile posterior subcapsular lenticular opacity (Farschtschi *et al.,* 2020). Tuberous Sclerosis Complex (TSC) is defined by the development of hamartomas in organ systems involving the skin, brain, kidneys, heart & lungs. It is characterized by cutaneous findings such as facial angiofibroma, nails, ungual fibroma, hypo-pigmented skin patches and Cortical tubers, cutaneous changes include café-au-lait spots and hemangioblastomas (Islam, 2021). Sturge Weber Syndrome is diagnosed with facial port-wine stain, leptomeningeal angiomatosis, and ipsilateral glaucoma. Its neurological complications are characterized by seizures, mental retardation and hemiparesis (Yan *et al.,* 2022).

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The clinical phenotype of Ataxia Telangiectasia includes the combination of progressive cerebellar ataxia, oculocutaneous telangiectasias, immunodeficiency, and an increased predisposition for malignancies. Telangiectasias on the face, ears and arms are some skin manifestations (Amirifar *et al.,* 2020; Amirifar *et al.,* 2019). NF1 and TSC are most frequently inherited in the autosomal dominant trait (Tolliver *et al.,* 2022). While ataxia, telangiectasia is inherited in an autosomal recessive manner, characterized by recurrent omphalitis and sinopulmonary infections (Rothblum-Oviatt *et al.,* 2016). In autosomal recessive inheritance, both genes of the individuals in each pair have to be recessive and altered to result in a disease. When both partners are affected, the risk is passed on to children, and they stand a 25/100 chance of having the disorder. Some neuro-cutaneous syndromes are sporadic, like SWS, although a genetic predisposition might be present in rare cases (Tamburrini & Di Rocco, 2010). Such cases are often random, associated with new mutations that the child inherits and that are not genetically inherited from either parent. Occasionally, they are caused by genetic mosaicism, meaning the mutation can be detected in only some of the body's cells (Awaad & Awaad, 2018). The present case series aimed to study the clinical profile of children with Neurocutaneous syndrome and their various symptomatology, the seizer type and response to the treatment.

CASE SERIES

This descriptive study was conducted in the Department of Pediatrics, Pushpagiri Medical College Hospital in Tiruvalla, India, from January 2013 to June 2013. After obtaining

approval from the Pushpagiri Medical College Hospital, affected children with different forms of NCS between the age group of 0-15 were included based on standard diagnostic criteria for various types of NCS. Informed consent was obtained from the parents of affected children. The study population comprised 10 children subjected to this prospective observational study. The diagnosis of various forms of Neurocutaneous syndrome was established among infected children through Computer Tomography, magnetic resonance imaging, electroencephalography, and skin biopsy for accurate diagnosis. The patients with Sturge Weber syndrome were diagnosed with the port-wine birthmark on their faces with glaucoma. Generalized tonic-clonic seizures (motor seizures) were considered as the first neurological manifestation of SWS diagnosis and 50% partial seizures. Children with several cafés au lait spots, light brown to dark brown, on different body parts, specifically on the trunk and extremities, were diagnosed with neurofibromatosis based on the age parameter; either these spots were aroused before puberty or after. It is a genetic condition caused by the mutation in the NF1 gene of 17 numbered chromosomes. However, this genetic protein controls and regulates cell growth, while its mutation can cause uncontrolled cell proliferation.

Children who present with Hypomelanosis of Ito's have skin colour loss that appears patchy and is referred to as Hypomelanotic patches, typically following the lines of Blaschko. These patches usually manifest very early in life or at the time of birth at the latest. In addition to the cutaneous symptoms, the children may become mentally disabled or may develop epilepsy. The diagnosis of Hypomelanosis of Ito is clinical; skin patterns that include grey-blue skin pigmentation and neurological symptoms associated with the condition will confirm the disease. Other diagnostic tests that can be carried out to diagnose mosaicism mean that individuals originating from single fertilized eggs have different cell populations genetically. These mutations occur during embryonic development after fertilization, and chromosomal abnormalities can be detected in 9, 15, 18 and 22, resulting in trisomy and monosomy conditions. The genes involved in melanin's biosynthesis pathway are specifically mutated, such as TYR, TYRP1, DCT, MITF, OCA2, and SLC45A2.

Tuberous sclerosis complex in children was diagnosed with a variety of symptoms through distinctive skin lesions. Oval, white and leaf-shaped patches appeared on their skin with facial angiofibromas, specifically of cheeks and nose, while shagreen patches on the lower back parts of the body and periungual fibromas around their nails. However, it was found that neurological symptoms were presented with every kind of Neurocutaneous disease, including general tonic-clonic seizures with partial seizures; it can begin in infancy with autism spectrum disorder. Additionally, sometimes benign tumours in different organs may be detected, including cardiac rhabdomyoma, renal angiomyolipomas, lymphangioleiomyomatosis, and retinal hamartomas, with cystic kidney and renal manifestations. TSC1 and TSC2 are two genes that, if mutated, cause Tuberous Sclerosis Complex (TSC), a genetic disorder that causes benign tumours to grow in several of the body's organs. The TSC1 gene on chromosome 9 codes for hamartin; the TSC2 gene on chromosome 16 codes for tuberin. It also forms a complex which aids in controlling cell division and specialization through the repression of the mammalian target of the rapamycin proteins that are essential to cell division and growth. Some mutations in TSC1 or TSC2 genes can inactivate hamartin-tuberin's complicated function. It results in geographic enlargement, uncontrolled cellular proliferation and the development of benign tumours or hamartomas in such body organs as the brain, skin, kidneys heart and lungs. In the case of TSC1-deficiency, the clinical outcome is less severe, whereas more significant disease manifestations characterize patients with TSC2-deficiency. However, depending on the person, these symptoms' clinical manifestation may differ.

These genetic mutations are genetic and inheritable; the disorder is autosomal dominant, which indicates that only one gene in a pair needs to be mutated for the disease to manifest. Nonetheless, the vast majority of TSC patients experience this disease as a result of new mutations when there is no background in the family. Infants and affected children with Incontinentia pigmenti, also known as Bloch-Sulzberger syndrome, underwent diagnostic manifestations. The first stage involves the development of small vesicles or bullae within the first days of life, located on the limbs and the trunk in Whorled lines, referring to Blaschko's lines. These changes evolve to the verrucous stage with wart-like hyperkeratotic lesions, then to the hyper-pigmented stage of swirling or streaked blue-grey or brown macules. These skin changes are important for the clinic and are usually supported by dermatological examinations and skin biopsies, microscopy reveals histopathological changes such as eosinophilia and dyskeratosis. Besides skin manifestations, IP can also impact other organs such as teeth and their eruption is delayed or has an incorrect shape; hair is sparse or comes in patches; nails may be pitted and ridged; eyes may have retinal changes and cataracts. Other symptoms may include neurological signs such as seizures and developmental problems requiring neurological examinations. This is so because by conducting the genetic test, one confirms that the child has an IKBKG (Inhibitor of Kappa Light Polypeptide Gene Enhancer in B Cells Kinase Gamma) gene mutation, which encodes for a protein that regulates immune response and cell survival. Management is oriented toward symptom control and is dedicated to each sign, orchestrating irrespective of the disease's aetiology, as IP is associated with numerous clinical signs.

RESULTS

A total of 10 children were included in the study, of which 5 were boys and 5 were girls, with an age range of 0-15 years, with a mean age of 7.5 years. Among 10 patients, four cases were of Sturge Weber syndrome, two were neurofibromatosis (NF-1), two were Hypomelanosis of Ito, one was Tuberous sclerosis complex, and one was Incontinentia pigmenti. Sturge Weber syndrome in four children presented with non-neoplastic congenital dermal capillary hamartomatous malformation, as depicted in Figure 1. They had neurological symptoms with generalized tonic-clonic seizures with muscle stiffness and rhythmic jerking movements, and 50% partial/ focal seizures with symptoms such as tingling, sweating, flushing, unusual sensation or numbness and lips smacking and 25% developmental delay was reported. Neurofibromatosis type 1 is a disorder of genetic inheritance in children, and the following case reports depict two children with mild symptoms of the disease; each child had café au lait spots, illustrated in Figure 2. Neurological manifestations included major seizures, particularly generalized tonic-clonic seizures, which were noted in 50% of the children together with developmental

delay in 50% of the same children and lich nodules were identified in their eyes.

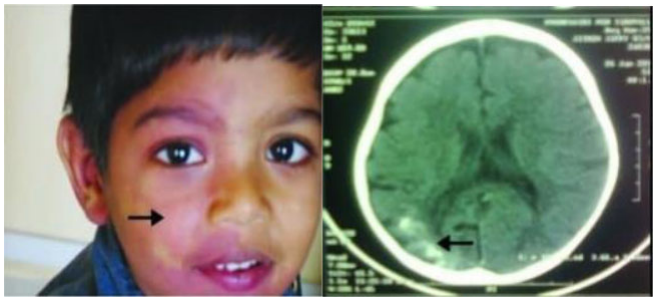

Figure 1. Port Wine Stain Lesions in Sturge-Weber Syndrome with CT-Scan

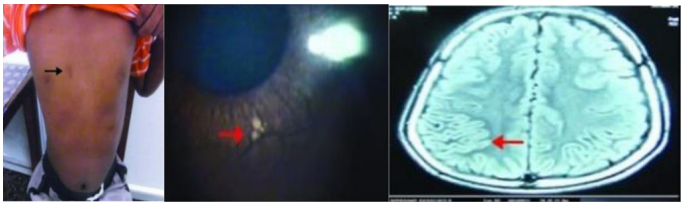

Figure 2. a) Neurofibromas on the body of affected child b) lich nodules in eyes c) CT-Scan

Hypomelanosis of Ito affected two children out of ten; they experienced 50% generalized tonic-clonic seizures, and developmental delays were reported in both of them. Both individuals had distinct cell lines at the back of their bodies due to post-zygotic mutations; these genetic changes affected their skin pigmentation, as shown in Figure 3 and its CT-Scan presented in Figure 4.

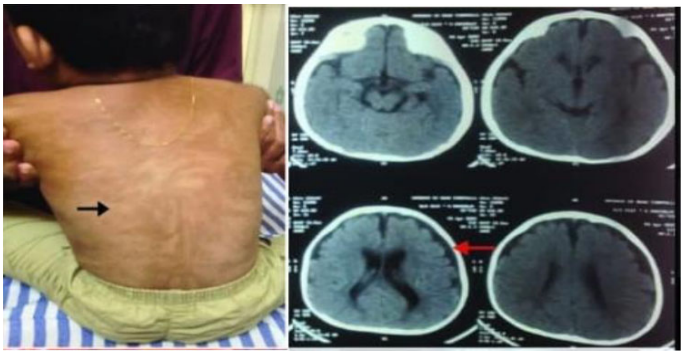

Figure 3. Patches of Hypomelanosis of Into with CT-Scan

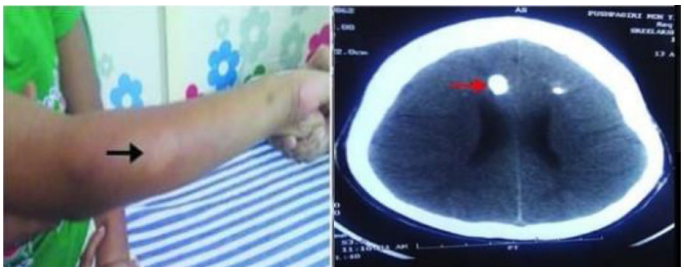

Figure 4. Tuberous Sclerosis Patches on Elbow with CT-Scan

However, maximum developmental delays were seen in Hypomelanosis of Ito, and its family history was found in two cases with 50% NF-1 and 100% IP. Tuberous sclerosis complex was confirmed in the child with hypomelanotic macules or 'ash leaf spots' and other skin lesions like the 'shagreen patches' and 'facial angiofibroma'. The child also had focal seizure, hypopigmented streaks and patches in a 'whorl-like' distribution typical of HI with 100% developmental delays. These are symptomatic patches, otherwise known as Ito patches, which are common skin abnormalities represented in TSC and come in different sizes and shapes may be in Blaschko's line considering the relevant mosaicism in this condition. TSC was caused by mutations of either the TSC1 gene on chromosome 9, which encodes hamartin or the TSC2 gene on chromosome 16, which encodes tuberin. These proteins combine to suppress the mammalian target of rapamycin or mTOR, which is known to manage cell growth and division. Abnormality of any of these genes halts the function of the p53 protein, thus allowing for continuous activation of the mTOR, which in turn produces benign tumours or hamartomas in many tissues and organ systems. In the skin, this presents as Hypomelanotic macules and other features on the skin, hair or nails. This condition can range from severe neurological and systemic manifestations to mainly dermatological involvement (Caban *et al.,* 2016). One child was diagnosed with Incontinentia Pigmenti who exposed the symptoms that are usually reported in affected patients but had no developmental issues. Characteristic symptoms were demonstrated in that child, such as blistering and wart-like rashes after birth, followed by hypopigmented swirls and streaks, as shown in Figure 5. Despite these manifestations, no signs of developmental delays were found.

DISCUSSION

Neurocutaneous Syndrome is a group of genetic infectious that includes Neurofibromatosis, Tuberous sclerosis complex, Sturge Weber syndrome, Hypomelanosis of ITO and Incontinentia pigments and affects the skin and nervous system. The present study was a prospective observational case series carried out among 10 children with different forms of NCS seen and managed at Pushpagiri Medical College Hospital, Tiruvalla, India, with ages ranging from 0-15 years with a mean age of 7.5 years, indicated four children diagnosed of Sturge weber syndrome, two children with neurofibromatosis (NF-1), two children with Hypomelanosis of Ito, one child with Tuberous sclerosis complex, and one child with Incontinentia pigmenti. These conditions were diagnosed by previous analysis by computer tomography, magnetic resonance imaging, electroencephalography, and skin biopsy.

Sturge Weber syndrome was reported in four children with dermal capillary non-neoplastic hamartomatous malformation, neurological manifestations, and or developmental delay of 25%. According to Anne M. Comi *et al.,* Sturge-Weber syndrome development is related to the extent of birthmark; they established that 15–50% is its probability in children. Laser therapy, eye drops, surgery, high-dose antiepileptic therapy, low-dose aspirin therapy, and neurosurgical intervention are the early interventions in managing a patient (Comi, 2015). NF-1 is a hereditary disease in children and two of them showed mild manifestations and café au lait macules. N Divakar discovered that 72% of NF1 patients had generalized tonic-clonic seizures (GTCS), while 28% had focal seizures. It means a high rate of generalized tonic-clonic seizures reported in NF1 (Divakar, 2014). K. Ina Ly, MD et al. suggest that if neurofibromatosis is symptomatic or disfiguring, it should be treated with electrodesiccation, CO2 laser treatment, surgical removal, or clinical trial (Ly & Blakeley, 2019).

Two children had Hypomelanosis of Ito; one had GTCS 50% and developmental delay, and the other also had developmental delay. Andrea Domenico Praticò et al. discovered that epileptic seizures in patients with HI disorder have been reported, but there is limited focus on the type, frequency, and treatment response. In five patients, the seizures manifested differently, with two being generalized (GTCS) and three of the focal motor complex. Two patients also showed mild cognitive delay, and one showed cerebral MRI dilation of the cisterna magna (Pavone *et al.,* 2015). Margie Ream et al. found that Hypomelanosis affects multiple organ systems, including the musculoskeletal, cardiovascular, brain, teeth, eyes, and kidneys can cause neurologic complications like seizures, tone abnormalities, and developmental delay. However, genetic mosaicism is its likely cause. Its management is symptomatic, but regular growth evaluation, neurodevelopment, and endocrine status are recommended (Ream, 2015).

Tuberous sclerosis complex was diagnosed in one child with hypomelanotic macules, ash leaf spots and other skin manifestations. The child similarly had focal uropathy and zones of hypopigmentation that appeared in a whorl-like regularity and distribution as that seen in HI; this child had 100% developmental delay. Darcy A. Krueger et al. discovered that TSC-associated neuropsychiatric disorders (TAND) are a significant aspect of TSC, affecting behavioural, psychiatric, intellectual, academic, neuropsychological, and psychosocial difficulties. The TAND Checklist was developed in 2015 to identify neuropsychiatric concerns in individuals of any age. Patients should receive a comprehensive assessment for TAND manifestations to identify areas needing immediate or early intervention. Kidney evaluation using abdominal imaging is crucial for identifying angiomyolipoma, while clinical assessment for lung abnormalities and chest CT is recommended for all females and symptomatic males. A comprehensive dermatologic evaluation by an experienced specialist is recommended for all patients, with Wood's lamp for detecting hypomelanotic macules and sun protection for adults and children. Age-appropriate cardiac assessment, including echocardiography and 12- to 15-lead ECG, is recommended for pediatric patients. A baseline ophthalmologic evaluation is also recommended for all individuals diagnosed with TSC (Northrup *et al.,* 2021).

TSC is a disorder attributed to the mutation of two genes: the TSC1 gene, located at chromosome 9 and codes for hamartin, and the TSC2 gene, located at chromosome 16 and for tuberin. These proteins combine to inhibit the mammalian target of rapamycin or mTOR, which is said to control cell treatment and replication. Dysregulation of any of these genes leads to the non-functionality of the p53 protein, which in turn can constantly stimulate the mTOR activity, which builds up benign tumours or hamartomas in the body in different tissue and organ systems. There is the case of a child with Incontinentia Pigmenti, the parents of whom described symptoms such as blisters and warty skin lesions after birth, hypo-pigmented swirls and streaks. Scheuerle et al. discovered that Incontinentia pigmenti leads to linear hypopigmentation, abnormal tooth shape, alopecia, dystrophic nails, hypodontia, retinal detachment, seizures, and intellectual disability, with some individuals experiencing retinal neovascularization; however developmental delays were occasionally seen (Scheuerle & Ursini, 2017).

Limitations

The study's small sample size of 10 children may limit statistical power and detect less common NCS subtypes. It also raises the risk of selection bias, as participants may not fully represent the broader NCS population. Findings may not apply to larger, diverse populations or represent NCS variability. Caution is needed in interpreting findings, as the small sample size increases the likelihood of chance findings. Limited resources may limit the scope of investigations, impacting the comprehensiveness of study outcomes.

Conclusion

The prospective observational case series provided insights into the various spectrum of Neurocutaneous syndromes observed in children. Sturge Weber syndrome, Hypomelanosis of Ito, Incontinentuia Pigmenti, Neurofibromatosis, and Tuberous Sclerosis complex were encompassed in the study. SW was evidenced with severe neurological features along with developmental issues, hence requiring multiple forms of therapies. As for NF-1 exhibited a remarkable prevalence of GTC, and Hypomelanosis of Ito presented multi-organ involvement, including neurological symptoms. Tuberous sclerosis complex, found in 1 patient, is associated with severe developmental impairment and dermatological manifestations underlining the genetic complexity and clinical presentations of TSC. As for dermatology, Incontinentia pigmenti displayed skin characteristics in its presentation. This series stresses the need for early detection, identifying individual care approaches, and interference that could be given to improve the lives of children with NCS.

Recommendations

It is recommended to enhance collaboration between multiple medical centres to expand the sample size and improve the generalizability of findings on Neurocutaneous Syndromes (NCS). It will also conduct longitudinal studies to track NCS progression in children, implement standardized data collection protocols, establish a centralized patient registry, and provide educational resources and support networks for families affected by NCS.

REFERENCES

Amirifar, P., Ranjouri, M. R., Lavin, M., Abolhassani, H., Yazdani, R., & Aghamohammadi, A. (2020). Ataxia-telangiectasia: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management. *Expert review of clinical immunology*, *16*(9), 859-871.

Amirifar, P., Ranjouri, M. R., Yazdani, R., Abolhassani, H., & Aghamohammadi, A. (2019). Ataxia-telangiectasia: A review of clinical features and molecular pathology. *Pediatric Allergy and Immunology*, *30*(3), 277-288.

Awaad, Y. M., & Awaad, Y. M. (2018). Neuro-cutaneous Syndromes. *Absolute Pediatric Neurology: Essential Questions and Answers*, 467-488.

Caban, C., Khan, N., Hasbani, D. M., & Crino, P. B. (2016). Genetics of tuberous sclerosis complex: implications for clinical practice. *The application of clinical genetics*, 1-8.

Comi, A. M. (2015). Sturge–Weber syndrome. *Handbook of clinical neurology*, *132*, 157-168. Divakar, N. (2014). PO-0818 A Case Series Study On Clinical Profile Of Children

With Neurocutaneous Syndromes. In: BMJ Publishing Group Ltd.

Farschtschi, S., Mautner, V.-F., McLean, A. C. L., Schulz, A., Friedrich, R., & Rosahl, S. K. (2020). The neurofibromatoses. *Deutsches Ärzteblatt International*, *117*(20), 354.

Islam, M. P. (2021). Tuberous sclerosis complex. Seminars in pediatric neurology,

Ly, K. I., & Blakeley, J. O. (2019). The diagnosis and management of neurofibromatosis type 1. *Medical Clinics*, *103*(6), 1035-1054.

Northrup, H., Aronow, M. E., Bebin, E. M., Bissler, J., Darling, T. N., de Vries, P. J., Frost, M. D., Fuchs, Z., Gosnell, E. S., & Gupta, N. (2021). Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. *Pediatric Neurology*, *123*, 50-66.

Pavone, P., Praticò, A. D., Ruggieri, M., & Falsaperla, R. (2015). Hypomelanosis of Ito: a round on the frequency and type of epileptic complications. *Neurological Sciences*, *36*, 1173-1180.

Ream, M. (2015). Hypomelanosis of Ito. *Handbook of clinical neurology*, *132*, 281-289. Rothblum-Oviatt, C., Wright, J., Lefton-Greif, M. A., McGrath-Morrow, S. A., Crawford, T. O., and Lederman, H. M. (2016). Ataxia telangiectasia: a review. *Orphanet Journal of Rare Diseases*, *11*, 1-21.

Ruggieri, M., Polizzi, A., Marceca, G. P., Catanzaro, S., Praticò, A. D., & Di Rocco, C. (2020). Introduction to phacomatoses (neurocutaneous disorders) in childhood. *Child's Nervous System*, *36*, 2229-2268.

Scheuerle, A. E., & Ursini, M. V. (2017). Incontinentia pigmenti.

Tamburrini, G., & Di Rocco, C. (2010). Neurocutaneous Syndromes. In *Neurosurgery* (pp. 529-537). Springer.

Tolliver, S., Smith, Z. I., & Silverberg, N. (2022). The genetics and diagnosis of pediatric neurocutaneous disorders: neurofibromatosis and tuberous sclerosis complex. *Clinics in Dermatology*, *40*(4), 374-382.

Yan, H., Hu, M., Cui, Y., Li, L., & Liang, T. (2022). Clinical characteristics of infants with port-wine stain and glaucoma secondary to Sturge–Weber Syndrome. *BMC ophthalmology*, *22*(1), 260.

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