ECRONICON OPEN ACCESS

EC NEUROLOGY
Case Report

Phacomatosis: Case Report

Astudillo-Mariño Nicolay[1]*, Rodríguez-Abarca Pamela[2], Freitas-Leonardo Furtado[3] and Benavides-Fuentes Eliana[4]

[1]*Department of Pediatric Neurology, San Francisco de Quito Hospital (HSFQ), Quito, Ecuador*

[2]*Department of Pediatric Ophthalmology, San Francisco de Quito Hospital (HSFQ), Quito, Ecuador*

[3]*Department of Neuroradiology, Beneficiencia Portuguesa Hospital, Sao Paulo, Brazil*

[4]*Department of Pediatrics, San Francisco de Quito Hospital (HSFQ), Quito, Ecuador*

***Corresponding Author:** Astudillo-Mariño Nicolay, Department of Pediatric Neurology, San Francisco de Quito Hospital (HSFQ), Quito, Ecuador.

Received: July 09, 2018; **Published:** September 27, 2018

DOI: 10.31080/ecne.2018.10.00407

Abstract

The neurocutaneous syndromes are a heterogeneous group of diseases with progressive multisystem involvement. These syndromes have different etiopathogenetic ways with a variable evolution and prognosis. The clinical manifestations involve to the central nervous system and the skin. We report the case of a patient who has clinical and imaging data related to neurofibromatosis type I and tuberous sclerosis. These diseases are a group of genetic disorders inherited in an autosomic dominant fashion with incomplete penetrance and variable expression; or are secondary to the novo mutations.

Keywords: *Phacomatosis; Neurofibromatosis Type I; Tuberous Sclerosis*

Introduction

The neurocutaneous syndromes (NCS) are a group of genetic disorders inherited in an autosomal dominant fashion with incomplete penetrance and variable expression. Neurofibromatosis type I (NF1) is the most common one [1-3].

The NF1 is a progressive genetic disorder with multisystem involvement. It was described by von Recklinghausen in 1882 [2]. The incidence is approximately 1 in 2600 to 3000 individuals. One half of the cases are inherited or familial. The remainder are result of the novo mutations [4].

The affected gene is located at chromosome 17q11.2 (tumor suppression gene which encodes neurofibromin protein). The number of cases have similar proportions between genres and an ethnical preponderance was not been reported [1].

The diagnosis is based in the presence of two or more criteria of the National Institutes of Health (NIH) (1987), submitted to periodical reviewing (Table 1) [2].

At least two of the following items
Six or more café-au-lait spots more than 5 mm in diameter in children and more than 15 mm in diameter in adolescents
Axillary and inguinal freckling (Crowe's sign)
Two or more neurofibromas or one plexiform neurofibroma
Optical pathway glioma in imaging studies
Two or more Lisch nodules in the ophthalmic examination with slit lamp
Bone lesions, sphenoid dysplasia, thickening of the long bone cortex and pseudoarthrosis
First degree relative with diagnosis of NF1

Table 1*: *Diagnostic Criteria for diagnosis of Neurofibromatosis Type 1 (NF1).*Taken from: Verdú* Pérez, Alfonso. *Síndromes neurocutaneos y otros trastornos relacionados. Manual de Neurología Infantil. p263.*

Café-au-lait spots are light brown color macules with fusiform, rounded or oval form, well-defined borders and variable size. The presence of café-au-lait macules is highly suggestive of the disorder.

Freckling are smaller macules of 2 - 3 mm in diameter that are localized in the inguinal and axillar region. It is also a classical sign of NF1 [5,6].

The neurofibromas are benign peripheral nerve sheath tumors. They are in the skin, subcutaneous region or could be deeper inside. There are comprised of Schwann cells, fibroblasts, and perineurial cells [2,7].

Lisch nodules are the classic ophthalmologic sign of NF1. There are pigmentary lesions of the iris that constitute melanotic hamartomas [8]. Lisch nodules tend to appear after six years and increase in number with age [9-11].

The report of seizures is associated with hemispheric tumors in a 5% of the cases that responds favorably to the treatment with ant seizures drugs [1].

Tuberous sclerosis complex (TEC) is an autosomic dominant fashion inherited disease. TEC has a multisystem involvement that affects the brain, skin, kidneys, eyes and heart where can produce multiple benign hamartomas.

At present, it is estimated that for each 6,000 to 10,000 live births, one is affected [2,3]. Two thirds of the cases are the novo mutations. Mutations in two different genes have been identified: TSC1 gene, located in the 9q34 chromosome and TSC2 gene, located in the 16p13.3 chromosome. TSC1 encodes a protein called hamartin that is responsible of produce complexes with tuberin protein encoded in the TSC2 gene [3]. The inactivation of both genes must occur for the clinical expression of the disorder [3].

The diagnostic criteria is shown in the table 2 [1]. STC is characterized by the classic triad of intellectual disability, seizures and sebaceous adenoma. This triad is present in almost one third of the patients. The most common clinical manifestations are in order of frequency: skin lesions (90%), brain lesions (90%), kidney malformations (70 - 90%), retinal hamartomas (50%), and rhabdomyomas (60%) [3,10,12].

Major criteria
Face angiofibromas
Non-traumatic nail fibroma
Three or more hypomelanotic spots
Shagreen plate
Multiple nodular retinal hamartomas
Cortical tubers (glioneuronal hamartoma)
Subependymal nodules
Subependymal giant cells astrocytoma
Cardiac rhabdomyoma. One or multiple
Lung lymphangioleiomyomatosis
Renal angiomyolipoma
Minor criteria
Dental enamel dysplasia
Rectal hamartomas polyps
Bone cysts
White matter radial migration lines
Gingival fibromas
Non-renal hamartomas
Achromic retinal plate
Confetti-like skin lesions
Multiple renal cysts

Table 2*: *Diagnosis criteria for tuberous sclerosis.*

Confirmed TEC: 2 major criteria (except for renal angiomyolipoma or lymphangioleiomyomatosis) or 1 major + 2 minor criteria. Probable TEC: 1 major + 1 minor criteria. Possible: 1 major or 2 or more minor criteria

**Taken from: Verdú* Pérez, Alfonso. *Síndromes neurocutaneos y otros trastornos relacionados. Manual de Neurología Infantil. P 263.*

The most common anatomic lesions of the central nervous system are the cortical tubers. They are present in 90% of the patients. Glioneuronal hamartomas are a kind of cortical focal dysplasia associated with disturbances in white matter, seizures, behavioral problems and learning impairment [3,4].

The most common findings in Computed Tomography CT scan include non-calcified cortical tumors with fatty content inside (tubers). This images in MRI are seen like hyperintense lesions in T1 sequence [3,13].

In those individuals who have a high compromise of the central nervous system and kidneys, the short term prognosis is dark and risk of death is high [3,14].

Case Report

Male, 7 years old. His grandfather was diagnosed (not confirmed) of NF1, now death. Personal background: sublingual frenulum resolved with surgery at 8 months old and learning disabilities. At 7 years starts with tonic and clonic seizures with eye deviation, consciousness impairment of 5 minutes long, followed by a post-ictal episode of 2 minutes long. He received ant seizure medication (carbamazepine), nevertheless, he has 2 new episodes of seizures like the described. At the physical exam: there are 7 hyperpigmented macules, of well-defined borders, different sizes (café-au-lait spots) localized in the neck, truncus and arms (Figure 1).

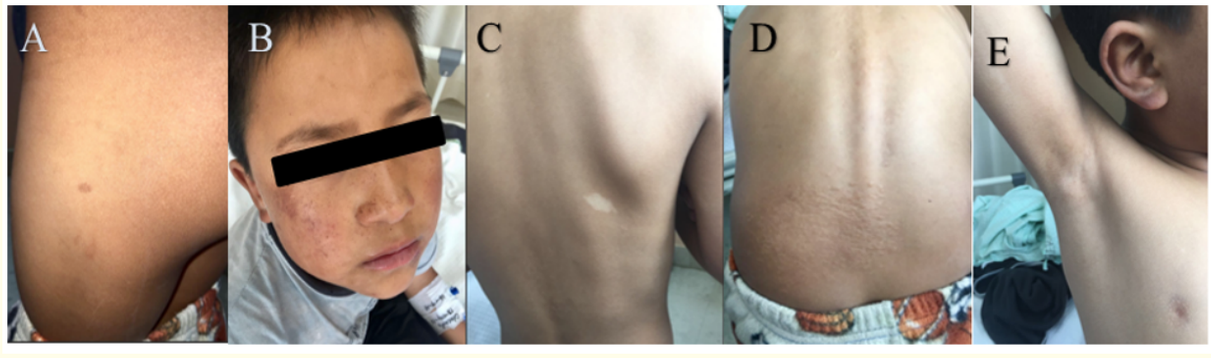

Figure 1: *a) Diffuse café-au-lait spots b) red papules localized in face c) 3 hypochromic lanceolate macules (ash leaf-like) localized on buttocks, leg and chest. d) elevated lesion formed by shiny achromic papules in lumbosacral region (Shagreen plate), e) axillary and inguinal freckling (Crowe's sign).*

Physical examination: neurocutaneous signs described above. Slit lamp: Both iris: rounded and pigmented lesions (Lisch nodules) (Figure 2).

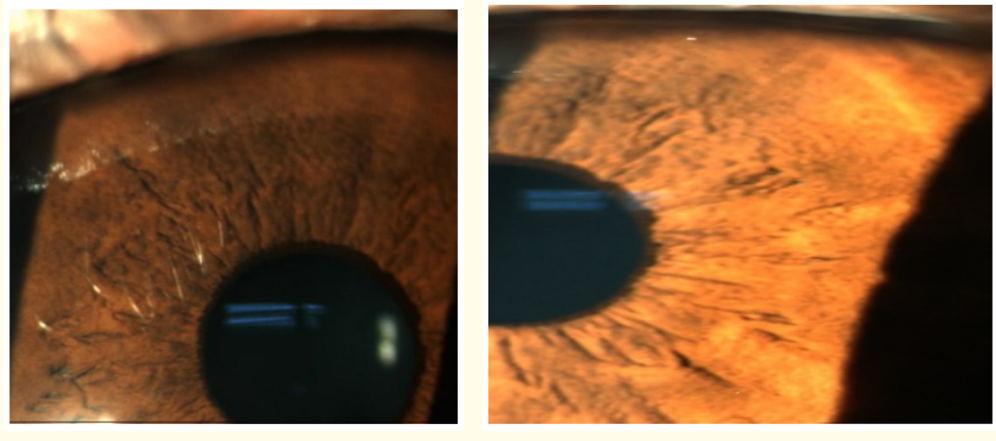

Figure 2: *Lisch nodules.*

Patient's diagnoses was Phacomatosis: Neurofibromatosis type 1 (more than six café au lait spots and Lisch nodules) and Tuberous sclerosis (facial angiofibromas, Shagreen plate, lanceolate hypochromic spots and cerebellum calcified tube. His seizures were controlled with valproic acid.

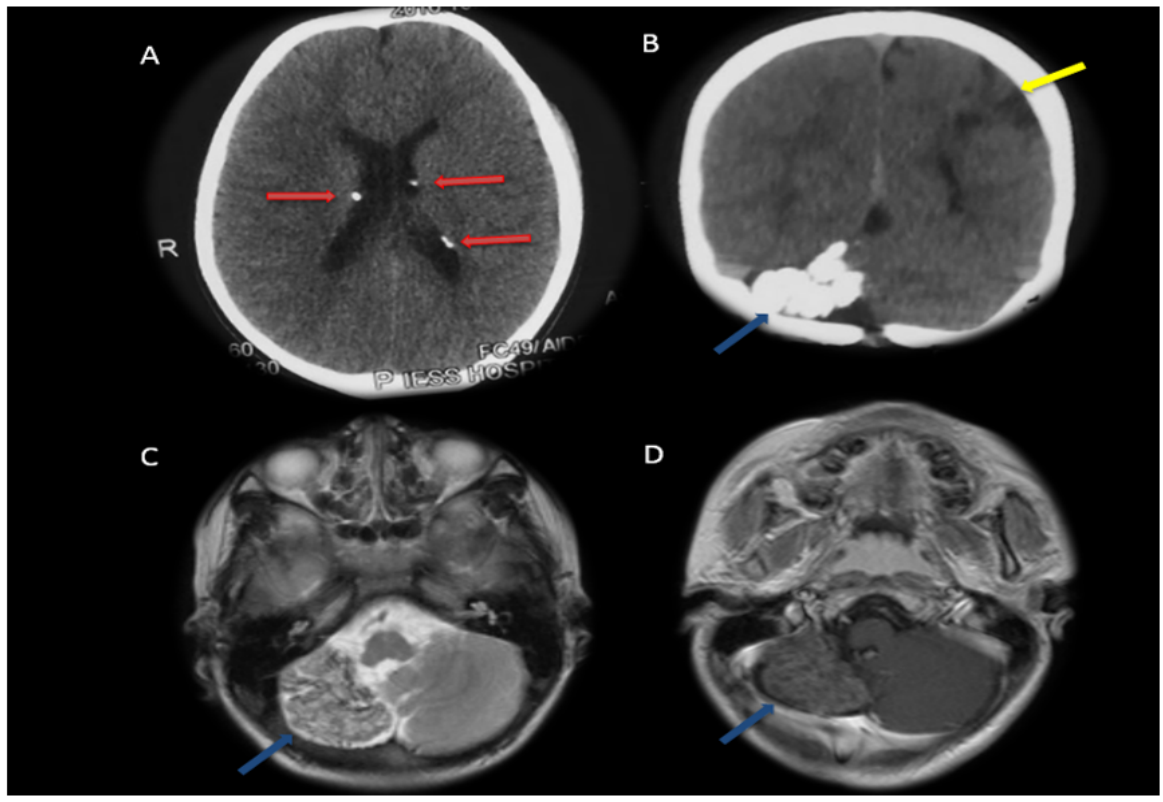

Figure 3: *CT scan (A) axial (B) coronal. MRI (C)T2 sequence and T1 (D) sequence Calcified subependymal nodules inside lateral ventricles (red arrows), cortical tuber with white matter radial migration line in left hemisphere (yellow arrows) Calcified tuber with contrast in right hemisphere (blue arrows). Right hemisphere is atrophied by lesion.*

Discussion

Phacomatosis is a genetic neurocutaneous disorder inherited in an autosomal dominant fashion with incomplete penetrance and variable expression. The diagnosis is based in the detection of typical clinical manifestations. The most common neurocutaneous disorder is NF1. The affected gene is located at chromosome 17q11.2. Patient of the Case 1 does not have a genetic study, however he has typical phenotypic characteristics like café-au-lait macules, axillary and inguinal freckling and Lisch nodules [2].

Tuberous sclerosis (TSC) is a disorder less common than tan neurofibromatosis type I. The affected gen is in the chromosome 9q34 (TSC 1), and in the chromosome 16p13.3 (TSC2). TSC1 encodes a protein called hamartin, which make complexes with tuberin protein (that is encoded in TSC2 gene). Like described above, we do not have a genetic study about TSC but the patient has a typical phenotype with facial angiofibromas, three hypopigmented spots and Shagreen plate. Furthermore, we can notice in imaging studies subependymal nodules, cortical tubers with white matter radial migration line, and a calcified tuber [5].

NF1 and TSC are two different neurocutaneous disorders. Rarely appears an association of them in one individual. In genetic study are mutation in both genes.

Random possibility of occurrence of a combined mutation is 1 in 12 to 27 million of people and the phenotypic expression is most extraordinary because to incomplete penetrance of NF1 and TSC [18].

The patient was admitted to hospital for presentation of seizures probably secondary to the evidence in imaging studies of a cortical tuber, subependymal nodule and white matter radial migration lines. The probability of seizures increases with the number of lesions. However, the response is good to ant seizures treatment [1,3].

There are few reports of a combined disorder. The firsts cases were described in 1968 and 1994. The report was based on clinical manifestations [16]. Later, are described cases of patients with clinical characteristics of both diseases and positive genetic study for the mutations [17].

Alaraj., *et al*. describe 11 cases in 2007. It was based in an exhaustive searching in Medline in studies from 1966 to 2006 (Table 3). According with the publication, the combined disorder was founded in Young people with familiar background of at least one of both diseases. In this way, 50% of cases was inherited and the other 50% was the result of the novo mutations [18].

On this way, Wheeler and Sadegui-Nejad, in 2005, report seven cases of a combined NF1 with TSC. The cases are the same of the study described above. The study of Sicilia., *et al*. is not included in the table, but it has an additional report of a combined case.

It is possibly that the combination of NF1 and TSC originate a more severe disease. We consider that our patient inherited the disorder of his grandfather. But, it was not possible to determine the severity of clinical presentation in the relative. Thereby is difficult to establish a prognosis in our patient based on his familiar background. However, it is necessary notice that exists an important intrafamilial and interfamilial variability for the clinical presentation.

Theoretically the combined genetic disturbance could lead to a severe phenotypical presentation, especially in the probability of tumor formation. However, this hypothesis could not be true, since a synergic effect was not described because the involved genes have opposed molecular functions [17,18].

According to the reviews, 13 cases have been reported to the moment, including the patient described in this paper. In the pediatric population (until 18 years old), only five cases have been reported.

On the other hand, the mutation of TSC2 gen is more severe than the mutation in TSC1 gene. As described above, the genetic study is not available, thereby is not possible to establish a prognosis.

Conclusions

- Neurofibromatosis type I and tuberous sclerosis are two different neurocutaneous disorders, and they rarely appear associated of them in one individual
- Both pathologies may cause seizures, in the case of tuberous sclerosis the probability of seizures increases with the number of lesions.
- There are very few cases of patients with these concomitant syndromes published and therefore this case is published in view of the need to know more about these pathologies.

Bibliography

1. PA Verdú. "Manual de Neurologìa Infantil, 2nd edition". Madrid (2014).

2. K Bruce. "Neurofibromatosis type 1 (NF1): Pathogenesis, clinical features, and diagnosis". Uptodate (2017).

3. Eduardo Núñez., *et al*. "Actualización de métodos diagnósticos en el Complejo de Esclerosis Tuberosa". *Revista Mexicana de Neurociencia* 17.4 (2017): 86-95.

4. MJN Fernandez Martin, *et al*. "Enfermedades neurocutaneas". Enfermedades Neurocutaneas Hospital de Guadalajara -España (2007): 87-92.

5. A Kramer Daniela and Po Patricia Muñoz. "Dermatología pediátrica latinoamericana". *Revista Oficial de la Sociedad Latinoamericana de Dermatologìa Pediíatrica* 10 (2012): 9-15.

6. Pablo Santana B., *et al*. "Neurofibromatosis tipo 1: una entidad fascinante. Reporte de 4 casos y revisión de la literatura". *Revista ANACEM* (2007): 52-54.

7. A Duat Rodríguez., *et al*. "Características fenotípicas y genéticas en la neurofibromatosis tipo 1 en edad pediátric". *Anales de Pediatría* 83.3 (2014): 147-226.

8. Listernick R., *et al*. "Late-onset optic pathway tumors in children with neurofibromatosis 1". *Neurology* 63.10 (2014): 1944-1946.

9. María Victoria Moreno Londoño., *et al*. "Nódulos de Lisch y ultrabiomicroscopia". *Revista Mexicana de Oftalmologia* 88.4 (2014): 189-193.

10. Afsar CU., *et al*. "Neurofibromatosis type 1, gastrointestinal stromal tumor, leiomyosarcoma and osteosarcoma: four cases of rare tumors and a review of the literature". *Critical Reviews in Oncology/Hematology* 86.2 (2013): 191-199.

11. Edward DP., *et al*. "Congenital ectropion uvea and mechanisms of glaucoma in neurofibromatosis type 1: New insights". *Ophthalmology* 119.7 (2012): 119:1485.

12. Luna Xu., *et al*. "Infrared Imaging and Optical Coherence Tomography Reveal Early-Stage Astrocytic Hamartomas Not Detectable by Fundoscopy". *American Journal of Ophthalmology* 153.5 (2011): 883-889.

13. Falsafi P., *et al*. "A Case of Tuberous Sclerosis Without Multiorgan Involvement". *Global Journal of Health Science* 7.5 (2015): 124-131.

14. Erol İ., *et al*. "Tuberous sclerosis complex; single center experience". *Turkish Archives of Pediatrics* 50.1 (2015): 51-60.

15. Girard N., *et al*. "Magnetization transfer in the investigation of patients with tuberous sclerosis". *Neuroradiology* 39.7 (1997): 523-528.

16. PC Janeiro., *et al*. "Ocurrencia simultánea de neurofibromatosis y esclerosis tuberosa, adquiridas como neomutaciones". *Revista de Neurología* 46.6 (2008): 347-350.

17. PG Wheeler and Sadeghi-Nejad A. "Simultaneous Occurrence of Neurofibromatosis Type 1and Tuberous Sclerosis in a Young Girl". *American Journal of Medical Genetics Part A* 133A (2005): 78-81.

18. Alaraj A., *et al*. "Double Phacomatosys; neurofibromatosis type 1 and tuberous sclerosis". *Acta Neurochirurgica (Wien)* 149.5 (2007): 505-509.

Volume 10 Issue 10 October 2018
©All rights reserved by Astudillo-Mariño Nicolay.*, et al.*