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Case Report

Legius Syndrome Vs Neurofibromatosis Type 1, About a Case Report

Yordania Velázquez Avila*, Carmen Rosa Rodríguez Valenciano

Service of Dermatology, Pediatric Hospital "Martyrs of Tunas", Tunas, Cuba

Abstract

The genodermatoses is genetic diseases that affect to the skin and their old ones, in those which alone they influence hereditary mechanisms linked to the genes. The neurofibromatosis type 1 are a genodermatoses that belongs to the group of the Rasophaties, with brown formation of stains with milk and tumours in skin and nervous system. This diseases can be diagnose clinically with the presence of two clinical approaches. In the year 2001 a Rasophatie was described that previously it was considered a clinical form of the neurofibromatosis, but it was demonstrated by means of molecular studies that it is a different diseases and it was designated as Legius syndrome. This syndrome completes two of the current diagnostic approaches of the neurofibromatosis type 1, when presenting coffee with milk macula and axillary or inguinal ephelides, being difficult to differentiate them. Although at the moment molecular studies of sequence exist for the diagnosis of both rasopatías, in some countries it is a non-available technology. In Cuba, like part of a methodology for the attention to patient with genodermatoses, the proposal of modification of diagnostic approaches of neurofibromatosis type 1 were included, unifying in one single approach the presence of coffee with milk macula and axillary or inguinal ephelides. The presentation is made with the purpose of standing out the importance of modifying the diagnostic approaches of neurofibromatosis type 1, proposed in the methodology. An adolescent is described that presented coffee with milk macula, axillary ephelides and overturn for deficit of attention with hyperactivity, assisted in specialized consultation of genodermatoses in the Pediatric Hospital "Martyrs of Tunas" with diagnostic presumptive of neurofibromatosis type 1. In the presented case the proposed approaches and the molecular study of neurofibromatosis type 1 negative, they guided toward the diagnosis of Legius syndrome. This case demonstrates the importance of the modification of the diagnostic approaches of neurofibromatosis type 1, proposed in the methodology for the attention to patient with genodermatoses that avoids the diagnostic error.

Keywords

Legius Syndrome, Neurofibromatosis Type 1, Rasophaties, Genodermatoses

1. Introduction

The genodermatoses are genetic diseases that affect to the skin and their old ones, in those which alone they influence hereditary mechanisms linked to the genes. [1] By means of advances in study of molecular sequence, they have been able to classify in several groups, among these they are the rasophaties, caused by germinal mutations of genes involved in the metabolic road RAS-MAP. The alterations dermatologics in the rasophaties can affect several areas of the skin, from the

*Corresponding author: yordaniacuba@gmail.com (Yordania Velázquez Avila)

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dermis until the epidermis, and to cause pigmented lesions, hyperkeratotic or hyperplastic. [2]

Two rasophaties exists clinically very similar, to present macula coffee with milk and axillary or inguinal ephelides: la NF1 o Von Recklinghausen ́s diseases (OMIM 162200 ORPHA 636) [3, 4] and Legius syndrome (OMIM 611431 ORPHA 137605). [5, 6]

NFI with inheritance AD affects the skin and the central and outlying nervous system; is due to a mutation in the gene NF1 located in the chromosome 17q11.2, encoder of a protein suppressor tumour, the neurofibromina, that participates in the control of the growth and the cellular differentiation. [7]

The diagnostic approaches were established for The National Institute of Health in Consensus Development Conferences in 1987, [8] and a proposal of their modification outlined for Vel ázquez at alt. in 2022, [9] and two should be completed or more than the following approaches:

1) Six or more coffee with milk macula of 5 mm in prepubertal patient and bigger than 15 mm en postpubertal or does witness of the Crowe ́s sign (axillary or inguinal ephelides).
2) Two or more neurofibromas, or a plexiphorm neurofibroma.
3) Glioma of the optic nerve.
4) Two or more hamartomas in the iris (Lisch ́s nodules).
5) Injure bony typical (Dysplasia of the wings esfenoidals or cortical weigh loss of long bones with or without seudoartrosis).
6) Family antecedents of NF1 in parents or siblings.

According to Brems and Legius, [10] in the year 2007 a mutation heterocigotic was identified in the gene SPRED1 located in the chromosome 15q, in 209 patients with diagnostic of NF1 like. This mutation implies function loss of one of the proteins implied in the road pathogenic RAS-MAPK, similar to the neurofibromina and for it shows it clinical similarities with the NF1, with the presence two approaches of those described for the diagnosis of NF1 what hinders the differential diagnosis among these two rasophaties.

To differentiate this disorder clinically indistinguishable with the NF1 that presents patron equal of inheritance AD, it was designated as syndrome of Legius, according to agreement of the 13th European Encounter on Neurofibromatosis. [11]

The NF1 has been more studied, being reported a prevalence of 1:3000 people according to Global NF Conference Highlights of 2024. [6] In relation to Legius syndrome international studies are not reported that infer their prevalence, being considered that of 1-4% of the cases diagnosed like NF1 correspond to Legius syndrome. [12]

In Tunas, in the oriental region of Cuba, was carried out in the year 2021 a study describing you rates prevalence for the NF1 of 20.,42:10,0000 peoples and Legius syndrome of 0.75:10,0000 peoples. [1]

Although at the moment molecular studies of sequence exist for the diagnosis of both rasophaties, in some countries it is a non available technology. In Cuba, like part of a methodology for the attention to patient with genodermatoses, the proposal of modification of diagnostic approaches of NF1 was included, unifying in one single approach the presence of coffee with milk macula and the axillary or inguinal ephelides. [1, 13] Next a case of Legius syndrome is described that presented clinical similarities with the neurofibromatosis type 1, with the purpose of standing out the importance of modifying the diagnostic approaches of NF1.

2. Case Description

Adolescent, feminine patient, 11 years old, urban origin that from the first months of life the mother noticed that she presented coffee with milk macula that it were being increased progressively so much in number like in size, being added small axillary ephelides around the 7 years, to this age was diagnosed of TDAH with difficulties in the academic use. With this square dermatologic arrives to the specialized consultation of genodermatoses in the Pediatric Hospital "Martyrs of Tunas" with diagnostic presumptive of NF1.

Personal antecedents: TDAH Family antecedents: father, paternal aunt and paternal grandmother with coffee with milk macula present, without defined diagnosis.

Reaction to medications: she didn't refer.

Dermatologic exam: manifestations cutaneous disseminated monomorfas given by coffee with milk macula and multiple axillary ephelides (Figure 1).

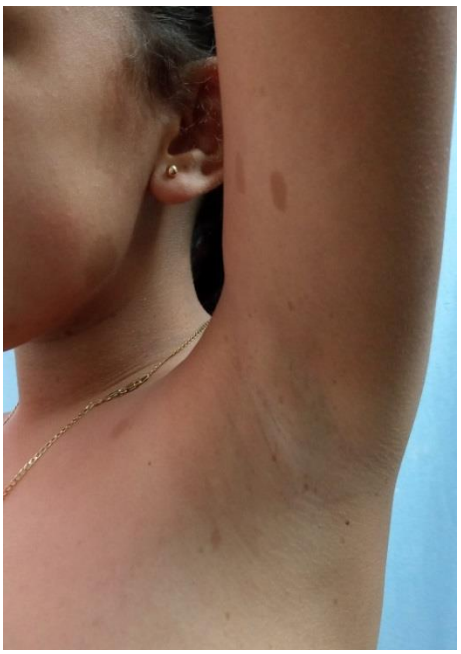

Figure 1. *Coffee with milk macula located in the face and left arm, accompanied by axillary ephelides (Crowe ́s sing). The authors' image, taken previous informed consent.*

Was carried out the genealogical tree (Figure 2) being determined an inheritance pattern AD that you correspondence

with the family clinic.

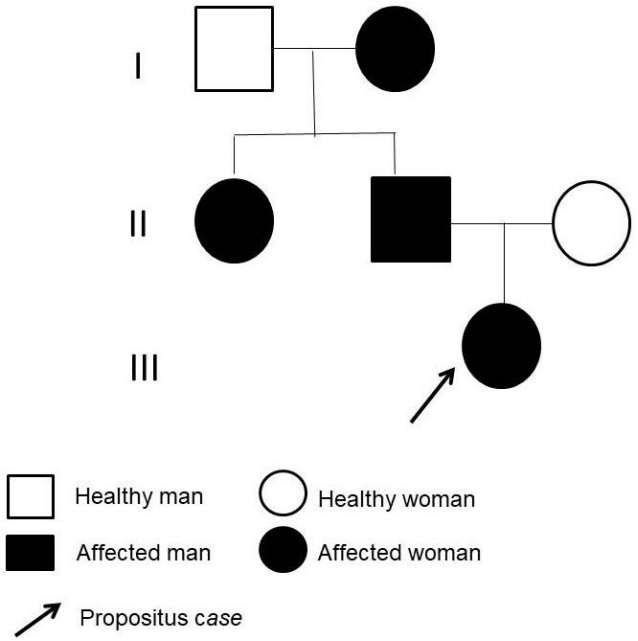

Figure 2. *Genealogical tree that pattern of inheritance AD shows. The authors' image.*

With these clinical manifestations it is thought of the possibility of NF1, for what they are carried out studies looking for other possible alterations.

Eye Fund: They were not observed Lisch ś nodules.

Nuclear Magnetic resonance of skull: Without alterations.

Study molecular indirect for NF1: negative.

In Cuba it doesn't have molecular study for the detection of the gene SPRED1, for what could not be carried out.

With the manifestations dermatologic, in absence of other signs of NF1 and with molecular study of NF1 negative was concluded as Legius syndrome.

Behavior: offered genetic consultantship to the family and attention multidisciplinary with dermatology, genetic, paediatric and psychologists. At the moment she is continued in consultation every 6 months, she has not presented complications and she has improved their academic yield with the educational support.

3. Discussion

"he diagnosis of NF1 is based on the recognition of at least two of the seven clinical approaches defined by the National Institute of Health. Although, the recognition of these approaches can be simple in the adult; in the children without family antecedents, it is more complex." [14]

The expresividad fenot ípica in the NF1 is very variable, even inside oneself family, and they are dependent of the age. It is important to keep in mind that the coffee with milk macula appear from the birth or the first months of life and they usually increase, so much in number as size, during the childhood; the plexiphorm neurofibroma is usually congenital; the gliomas of the optic nerve has been described starting from the two years; the axillary or inguinal ephelides are observed between the third and the fifth year of the life; the Lisch ś nodules appear among the five to six years of age. [15, 16]

Reason for the that in the methodology designed in Cuba, intends the molecular study around the 10 years old, if alone has shown the brown presence of coffee with milk macula accompanied by axillary or inguinal ephelides. [1]

The rasophaties, shares like base a deregulation of the road RAS/MAPK, they present multiple manifestations superimposed fenot ípicas, although with different expresividad and penetrancia, [17] for what should be carried out the differential diagnosis among them. The brown presence of stains with milk, concomitanting with congenital cardiovascular alterations, besides distinctive features, they can be in the NF1, el Noonan syndrome, LEOPARD syndrome, cardiofaciocutaneo syndrome and Costello syndrome. [17]

Legius syndrome is characterized by the presence of multiple coffee with milk macula and the axillary or inguinal ephelides, [18] accompanied by features dimorphic, lipomas in the mature age, dysfunctions of the learning, [19] but contrary to the NF1, it doesn't present cutaneous tumors, neither of the central nervous system, [18] for what neurofibromas, plexiphorm neurofibroma, gliomas of the optic nerve, neither Lisch ś nodules are not presented. [19]

In a patient with presence of coffee with milk macula and the axillary or inguinal ephelides, without other clinical manifestations it becomes difficult to distinguish if it is a NF1 of little expresividad or a Legius syndrome. Several authors have pled for the necessity of modifying the diagnostic approaches. In the year 2021 Legius et al, [12] they carried out a revision in which proposed that in individuals without family antecedents of NF1, besides fulfilling two approaches, a variant of the gene NF1 heterocigotic pathogenic should be identified with a proportion of the stupefy muted of more than 50% in seemingly normal fabric as the white globules; and in those descending of a progenitor that fulfills the diagnostic approaches of NF, there is not necessity to carry out the identification of the muted gene.

Duat et al. [14] y S ánchez, [19] in their investigations, in 2015 and 2021 respectively, they suggested the modification of the diagnostic approaches unifying the stains coffee with milk macula with axillary or inguinal ephelides. This same approach was proposed in a methodology for the attention to patient with genodermatoses in Cuba, being validated by means of the method experts' Delphi in 2021. [1, 9]

Although the sequence of new generation is the most robust molecular technique, it is unreachable for many laboratories of molecular biology. [20] In Cuba it is not had molecular studies for the diagnosis of the Legius syndrome, for what became necessary to carry out the molecular study of NF1 for indirect method using as marker a polymorphism of longitude of restriction fragment in the presented case (Rsa I NF1 ex ón

5). [21] When being negative, it was thought, for decantation that was the Legius syndrome.

In other investigations, strange authors, also carried out the diagnosis of Legius syndrome for decantation, after carrying out the genetic study of NF1. In the study of Duat, was carried out the direct study by means of a sieved mutational of ADNc *NF1* with technical of ARN (cDNA-DHPLC) combined with techniques based in MLPA with a sensibility of 95%, [14] and in Sánchez's investigation before a patient with stains and/or ephelides, was carried out molecular genetic study MLPA for NF1, and alone to those that were negative for NF1, they were enlarged the genetic study of Legius syndrome. [19]

The behavior before a patient with a rasophaties, such and like was carried out in the presented case, it consists on a pursuit multidisciplinary point for the patient's education and the family with the genetic advice, like to prevent and to treat possible complications. In the patients that TDAH presents or other dysfunctions cognitive should be continued with psychological therapies and differentiated educational support.

It is necessary of more scientific studies in relation to the Legius syndrome that they allow to know their incidence, possible signs and the symptoms associated of the diseases.

4. Conclusions

In the presented case the proposed approaches and the molecular study of neurofibromatosis type 1 negative, they guided toward the diagnosis of Legius syndrome. This case demonstrates the importance of the modification of the diagnostic approaches of neurofibromatosis type 1, proposed in the methodology for the attention to patient with genodermatoses that avoids the diagnostic error.

Abbreviations

RAS-MAPK	Mitogen Activated Protein Kinase
NF1	Neurofibromatosis Type 1
OMIM	Online Mendelian Inheritance in Man
ORPHA	Portal of Information of Strange Diseses and Orphan Medications
AD	Autosomal Dominante
TDAH	Overturn for Deficit of Attention with Hyperactivity
ADN	Deoxyribonucleic Acid
ARN	Ribonucleic Acid
DHPLC	Denaturing High Performance Liquid Chromatography
MLPA	Multiplex Ligationdependent Probe Amplification

Author Contributions

Yordania Velázquez Avila: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing

Carmen Rosa Rodríguez Valenciano: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing

Ethical Responsibilities

An informed consent form has been completed and signed by the legal representative (mother), and the research committee of the institution where the clinical history was taken has granted authorization, thereby ensuring the patient's right to privacy and guaranteeing the protection of his or her identity in accordance with international regulations.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Research Field

Yordania Velázquez Avila: Legius syndrome, Neurofibromatosis type 1, Rasophaties, Genodermatoses, Genetic diseases of the skin

Carmen Rosa Rodríguez Valenciano: Legius syndrome, Neurofibromatosis type 1, Rasophaties, Genodermatoses, Genetic diseases of the skin.