ISSN 2692-5877
DOI: *10.46998/IJCMCR.2020.01.000017*

International Journal of
Clinical Studies & Medical Case Reports

Review Article

Type 1 (NF1) Neurofibromatosis In Children: The Importance of Clinical Diagnosis

Arruda A[1], Pimentel D[1], Correa L[1], Pinho R[1], Melo KFL[3], Nobre AFS[3] and Alcantara DFA[2]

[1]Department of biology, Undergraduate students of the biomedicine course at Escola Superior Madre Celeste – ESMAC, Brazil

[2]Department of biology, Professor doctor at Escola Superior Madre Celeste – ESMAC and Researcher at Universidade Federal do Pará – UFPA, Brazil

[3]Department of biology, Professor at Escola Superior Madre Celeste - ESMAC, Brazil

[*]**Corresponding author:** Diego Alcantara, Department of Biology, Institute of Biological Sciences, Universidade Federal do Para, Brazil. E-mail: diegoalcantara@globo.com

Received: June 03, 2020 Published: June 29, 2020

Abstract

Neurofibromatosis type 1 (NF1) is a genetic disorder that has an autosomal transmission mode, which results from an abnormality of a dominant gene. The process of diagnosis and investigation of the disease is based on behavioral problems and bone changes in the orbital morphology of patients and family history. Thus, the aim of this study is to demonstrate the importance of early clinical diagnosis to improve the quality of life of patients affected by the disease. This is a retrospective study, based on the review of academic articles on the main research platforms such as Scielo, Pubmed and Lilacs. Publications between the years 2009 to 2020 were considered. The outlook today is to expand the information about the disease, so that people know how to minimize the negative impacts caused by it. The Neurofibromatosis type 1 (NF1) has no cure, and treatment has only aimed at improving the quality of life of sufferers and their families, which is very important to know how to deal with future complications of the pathology.

Key words: Neurofibromatosis; Neurofibromatosis type 1; Children; Skin Pathologies; Genetics; NF1; Clinical Diagnosis; Early Diagnosis and Prognosis

Introduction

Neurofibromatosis, also known as Von Recklinghausen's disease, is a set of pathologies, divided into symptoms and age, with type 1 (NF1), type 2 (NF2) and schwannomatosis involvement. NF1 occurs mainly in children – being considered the most incident in 90% of cases – while NF2 and schwannomatosis occurs more in adults. A syndrome affects the brain, spine, nerves and skin. NF1 indicates decreased quality and life expectancy for patients aged 8 to 21 years [1]. The disease is related to the appearance of symptoms as the age increases, and the main three (pigmented lesions, skin tumors and bone changes) are related to the age of 20, contributing to lethality. Neurofibromas, the formation of small nodules, is seen as late symptom, considered an important auxiliary for the diagnosis of the disease, but with failures, due to the need for early identification [2]. Shortly thereafter, the child may progressively experience paresthesia's and pain in the thoracolumbar region and in both lower limbs, as well as an increase in volume at the level of the entire right lower limb, which makes walking difficult. The process of investigating the disease is done through family history, through the study of the genetic alterations of the NF1 gene and the interconnected symptoms [3]. The diagnostic criteria are defined by clinical analysis, according to the process of the Children Medical Center, in the United States. Patients who have first degree of symptoms in NF1 contribute to the possibility of the criteria described above. The evolution of the pathology indicates paresthesia's and pain in the thoracolumbar region, with an increase in the volume of lower limb, making the walking process difficult [4].

Objective

The objective of this work is to review what would be Neurofibromatosis (NF1), the gene that occurs the mutation, symptoms, early diagnosis that is benefecial for children and the treatment that improves the patient's condition. It also seeks to expand the knowledge of patients and their families, since it allows them to provide ralatives with appropiate information to improve the quality of life for each of them. Demonstrate the importance of early diagnosis for improving the quality of life of patients with type 1 Neurofibromatosis.

Materials and Methods

This study was based on database analysis, such as Pubmed, Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs) and Scientific Electronic Library Online (Scielo). For data analysis, the following keywords were used: "Neurofibromatosis", "Neurofibromatosis type 1", "Children", "Skin pathologies", "genetics", "NF1", "Clinical diagnosis",

"Early diagnosis" "and" "Prognosis". The focus is the analysis of article published in the last eleven years (2008 – 2020), in English, Portuguese and Spanish. Studies have been studied that aim to describe and analyze the relationship "early diagnosis X improvement of patient's quality of life".

Development

Historic

The disease was first described in 1882, since then, several related discoveries of skin pathologies and behavioral issues. From the 90's, a study for specific diagnosis (because there are three diseases with some similar clinical characteristics) started, with the study for clinical-genetic characteristics. The disease is based on diagnostic criteria from the National Institute of Health. In 1998, the need for a diagnostic criterion was dictated for children under 6 years of age, because some symptoms can cause confusion among health professionals [5].

Incidence

NF1 is an autosomal dominant genetic disorder, with an incidence of approximately 1 to 3000 individuals. In some cases, the disease is related to a family case (inherited) while others indicate a mutation (sporadic), which are associated with errors that occur mainly in the paternal chromosomes, increasing the prevalence with advanced paternal age [6]. 50% of patients have a spontaneous mutation and the other half have an inherited mutation. It occurs equally between gender and race [7]. Evolution results in the deletion of the DKN2A/p16 gene, located on chromosome 17.

Symptomatology/Criteria for Diagnosis

Initially, behavioral problems occur, such as hyperactivity disorders and attention deficit (ADHD); Bone changes in the orbital morphology of patients with NF1, characteristics that contribute to the presence of hypertelorism, that malformation of the baby's skull; Biochemical evidence of deficiency in growth hormone, even with presence of receptors, resulting in a moderate increase in height, it helps, later, in the formation of osteoporosis or osteopenia; Decrease in bone mineral density in the lumbar spine and scoliosis [8]. NF1 can cause acute myeloid leukemia in its patients, but the most common cancers are brain tumors, in peripheral nerves and connective tissue tumors, due to the hyper proliferation of endothelial cells and pericytes, cells that line blood vessels. It occurs because it is a failure in signaling between Schwann cells, perineural cells and fibroblasts. All patients have a coffee-milk stain on their skin, melanocytes [9]. The diagnostic criterion for NF1 developed by the NIH consensus development conference, admits two or more of the following clinics:

1. Six or more MCCL with a diameter greater than 5mm in prepubertal individuals or above 15mm postpubertal individuals,
2. Two or more neurofibromas of any type or one plexiform neurofibroma, based on clinical and histological parameters,
3. Ephelids (freckles) in the axillary or inguinal region
4. Optical glioma
5. Two or more Lisch nodules (pigmented iris)
6. A distinct bone lesion such as pseudo arthrosis of a long bone or dysplasia of the sphenoid wing
7. A first-degree relative with NF1 who attend the preceding criteria.

The genetic (or molecular) test for NF1 identifies approximately 95% of the mutations in individuals who attend the clinical diagnostic criteria. Up to the age of 20, all patients attend 100% of the criteria [10].

Clinical Diagnosis

The process of investigating the disease is done through family history, through the study of the genetic alterations of the NF1 gene and interconnected symptoms. In children, the diagnosis is made by the initial analysis of height, weight, head circumference, evidence of normal sexual development, signs of learning difficulties and/or behavioral problems [11]. They should receive a skin exam to detect growths, blemishes, scoliosis, blood pressure, vision and screening hearing loss. In adults, also analysis of the standard characteristics and a skin exam to detect growths, spots, scoliosis, blood pressure, vision and screening for hearing loss. Genetics tests are performed during prenatal care [12].

Treatment

The pathology does not have a specific treatment, there is an improvement in the quality of life in the treatment of associated diseases, and prognosis of patients with tumors of the central nervous system (CNS) depends on the age of the patient, presence of symptoms related to neoplasia and tumor extra-optical. In some situations, lesion growths can be surgically removed or reduced with radiation therapy, but surgery in these areas can cause further nerve damage and additional neurological problems [13].

Perspectives

Currently, the dissemination of information about NF1 is scarce, both for patients and their families. With disinformation, it makes it more difficult to provide support and alternatives that are more effective in coping with it. The current perspective is to expand information about the disease, making people know how to minimize the negative impacts caused by NF1, and understand that early diagnosis helps in improving patients lives since childhood. The investigation of Neurofibromatosis type 1, as it is rare, is not so fast and seeks the attention of a well qualified professional that allows the definitive diagnosis of disease. Thus, investment in research and in the training of health professionals i salso of fundamental importance [14].

Results and Discussion

Neurofibromatosis type 1 has several manifestations among patients because of is mutation power, it is the most common human disease caused by a defect in a single gene. Although there is no specific treatment for NF1, the importance of early diagnosis through family history and clinical examinations is essential in children who have not yet entered puberty. The presentation oh the pathology is mild and moderate in common cases, severe in rare cases leading to death, the most severe forms appear after the wave of hormones at puberty. As the literature indicates, the main causes of death come from malignant tumors of the peripheral nerve sheath, optic gliomas that evolve aggressively and cardiovascular diseases, and, although the death rate affected by myeloid leukemia, breast cancer or any another type of câncer proves to be small, we must not rule out the danger of lethality. It is worth mentioning the family members of treated patient, who although possible complica-

tions of the disease can reduce their life span, they can live in a healthy way [15].

Conclusion

As it is a pathology that has no cure and variable clinical expression, the treatment of one patient does not include others, it is up to the health professional to respect the individuality of each affection arising from Neurofibromatosis type 1, giving priority not only cases serious, but also to mild and moderate cases. The monitoring of patients affected by NF1 is relevant, since life expectancy is reduced with each apprearence of symptoms of the disease. Early pathological diagnosis is of paramount importance so that the individual does not suffer such negative impacts over the years due to NF1.

References

1. Antônio JR, Goloni-Bertollo EM, Trídico LA. Neurofibromatosis: chronological history and current issues. An Bras Dermatol. 2013;88: 329-43.
2. Souza JF. Toledo LL, Ferreira MCM, Rodrigues LOC, Rezende NA. Neurofibromatose type 1: mais comum e grave do que se imagina. Ver. Assoc. Med. Bras. Minas Gerais, Brasil. v. 2009;55:394-9.
3. Bortoluzzi AS, Magnagnagno OA, Nobre LFM. Neurofibromatose type 1 -impactos na infância e na adolescência. Faz ciência. Porto Alegre, Rio Grande do Sul. 2017;19:29
4. Evans DGR, O'hara C, Wilding A, Ingham SL, Howard E, Dawson J, et al. Mortality in neurofibromatosis 1: in North West England: an assessment of actuarial survival in a region of the UK since 1989. European Journal of Human Genetics, Manchester, Inglaterra. 2011;19:1187–1191.
5. Rosa MLRBC. Neurofibromatose tipo 1: revisão geral a propósito de um caso raro de apresentação a nível abdominal e membros inferiores. 2015, 2016. Dissertação (Mestrado em Medicina) – Faculdade de Medicina – Universidade de Lisboa, Lisboa. 2016.
6. Korf BR, Waltham MA. Neurofibromatosis type 1 (NF1): Pathogenesis, clinical features, and diagnosis. In: T. W. Post (Ed.), UpToDate. 2018.
7. Cunha Filho JJ, Scortenagna A, Martins F, Schwengber MMB, Robinson WM. Neurofibromatose tipo 1 e suas manifestações bucomaxilofaciais. Revista de Odontologia da UNESP. 2008;37(3):283-289.
8. Espig AF, Slomp AA, Campagnnolo AQ, Rockenbach DM, Da Silva BD, Pomblum VJ. Neurofibromatose tipo 1: atualização. Rev Bras Clin Med. 2008;6:243-249.
9. Moraes FS, Santos WEM, Salomão GH. Neurofibromatose tipo I. Rev Bras Oftalmol. São Paulo, Brasil. 2013;72: 128-31.
10. Darrigo Junior LD, Filho ABD, Alessandro DSM, Geller M. Neurofibromatose tipo 1 na infância: revisão dos aspectos clínicos. Rev Paul Pediatr. 2008;26(2):176-82.
11. Marques AC, Dinis F. Neurofibromatose tipo 1: relato de um caso clínico. Rev Port Med Geral Fam. 2013; 29:322-6.
12. Ramírez TM, Chávez LG, Zamora JL. Neurofibromatosis tipo I. Presentación de un caso. Revista de Informátion Científica. Guantánamo, Cuba. 2019;98:3
13. Le C, Bedocs PM. Neurofibromatosis. StatPearls. [online]. Neurofibromatosis. Disponível em: 2018. <https://www.mayoclinic.org/diseases-conditions/neurofibromatosis/diagnosis-treatment/drc-20350495>. Acesso em: 26 de março de 2020.
14. Gonçalves MVC, Costa SM, Jamil LC, Oliveira KR, Botelho PPR, Versiani CM, et al. Neurofibromatose tipo 1 com acometimento do nervo infraorbital: relato de caso. Revista Brasileira Cirurgia Plástica. Belo Horizonte, Minas Gerais. 2019;34:552-55.
15. Souza JF, Toledo LL, Ferreira MCM, Rodrigues LOC, Rezende NA. Neurofibromatose tipo 1: mais comum e grave do que se imagina. Rev Assoc Med Bras. 2009;55(4):394-9.