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NEUROFIBROMATOSIS TYPE I - CLINICAL EVOLUTION AND PSYCHOSOCIAL IMPLICATIONS

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Abstract

Neurofibromatosis type I is an autosomal dominant neurocutaneous disease which affects about 1 in 3000-4000 individuals. It has a variable expressivity, even in the same family. The evolution may vary from a mild form, accidentally diagnosed, to a life threatening form. We evaluated the patients diagnosed in the Regional Center for Medical Genetics of Oradea, in order to see the clinical evolution and the psychosocial impact of neurofibromatosis type I. The study is a descriptive research, both retrospective and prospective, on 69 patients with minimum age of 14. The purpose of the research was to identify how many patients inherited the disorder from a parent and passed it on to their offsprings and what clinical evolution they had. We also followed the psychosocial impact of neurofibromatosis type I, by searching for the presence of cognitive deficit and learning disabilities, disability degree and invalidity pension, social integration or isolation and employment status.

Key words: neurofibromatosis, caf é-au-lait spots, Lisch, neurofibroma, glioma.

INTRODUCTION

NF I (neurofibromatosis type I) is a neurocutaneous genetic disorder, in which a mutation appears in a gene called NF1 on chromosome 17q11.2. This gene regulates the production of neurofibromin, which is a tumor suppressor (Abramowicz A, Gos M., 2014). The neurofibromatosis type I has full penetrance(Friedman JM, 1999) but variable expressivity, even in the same family, from mild phenotype with cafe-au-lait spots to very severe, life threatening phenotype, with optic pathway gliomas(Easton DF et al,, 1993). In light of the new molecular analysis possibilities (Shofty B.et al, 2015) pre- and postnatal diagnosis is improving patient's life. We evaluated the patients of the Regional Center for Medical Genetics of Oradea, in order to see the particularities of the clinical evolution and the psychosocial impact of neurofibromatosis type I.

OBJECTIVE

The purpose of this longitudinal study is to evaluate the clinical evolution particularities of the disorder in patients over a period of at least 14 years.

MATERIAL AND METHOD

The study is a descriptive research, both retrospective (study of the medical files) from 1983 to 2016, and prospective by complete clinical, paraclinical and imagistic evaluation, according to the recommendations (Ferner Re, Gutmann DH., 2013) from 2016 to 2018.

The patients were diagnosed in the Regional Center for Medical Genetics (previously Genetic Compartment of the Clinical Municipal Hospital of Oradea), using the clinical criteria (Gutmann DH et al, 1997). Since 1984 in the Regional Center for Medical Genetics 92 patients were diagnosed with NF I (1.85% of the total number of genetic disorders diagnosed in the Regional Center). A total of 69 patients with NF I, with the minimum age of 14 were followed-up from the diagnosis to the present.

RESULTS AND DISCUSSION

The distribution of patients by age seems to be heterogeneous, with few data before 1983, when the Genetic Compartment started its activity. (fig. 1).

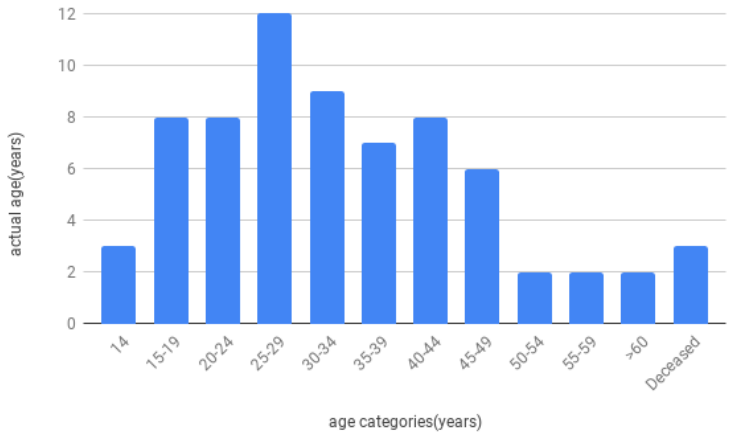

Fig. 1. Distribution of patients by age

By studying the diagnosis age we noticed that patients were diagnosed at different ages, most of them before age of 20 (57.97%). The

variable expressivity of the NF I is probably responsible for that, patients with mild phenotype are accidently discovered when they come to the specialist for another problem (Jurcă A et al, 2017). Sometimes, we discovered an entire family with mild phenotype behind one patient with severe phenotype (Kehrer-Sawatzki H.et al, 2017). (fig. 2)

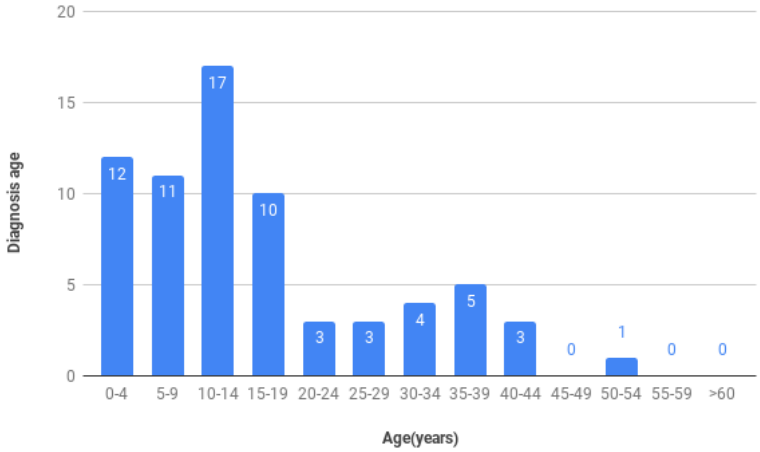

Fig. 2. Distribution of patients by age at diagnosis

Ussually about half of the affected individuals inherit the disease from their parents, as an autosomal dominant trait, the rest of the cases being the results of spontaneous (sporadic) mutations of the gene (Friedman JM, 1999). In our days, the molecular diagnosis can identify the mutation and clarify the diagnosis (Wu-Chou et al. 2018). In our study group 58% of the patients inherited the disorder from a parent and 37,5% of them passed it on to their offsprings. About three quarters of the pacients had at least one affected member of the family. (fig.3)

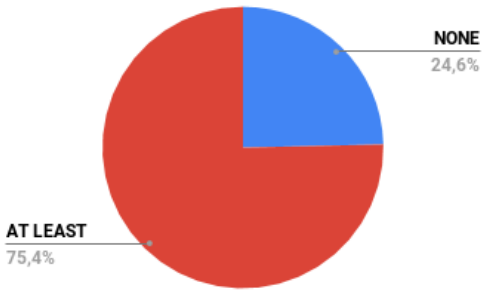

Fig.3 Patients with affected relatives

The evolution of the patients followed the known pattern (Jett K, Friedman JM., 2010) café-au-lait spots from birth or within the first year, which increased in size and number, followed by axillary and inguinal freckles by the age of 3 to 5 years (Lu-Emerson C, Plotkin SR., 2009). About a third (39.13%) of the study group presented cutaneous neurofibromas, but only 15.95% showed plexiform neurofibromas.

The risk of developing malignant tumors is higher in NF I that in the general population (Poyhonen M et al, 1997). Intracranial tumors (usually optic pathway gliomas) appears in some cases (Albers AC. Gutmann DH., 2009). In our group 5 patients (7.24%) had optical glioma and had surgery.

Commonly found in NF are scoliosis (dystrophic and nondystrophic), congenital pseudarthrosis of the tibia, and problems related to soft-tissue tumors (Feldman Dset al., 2010).13 patients from our group (18.84%) showed bone abnormalities like skeletal dysplasia and pathological fractures.

Others traits identified were: macrocephaly, hydrocephaly, Lisch nodules and cognitive deficits and learning difficulties, comparable to the published literature (Jurcă C. et al, 2017).

The mortality in our study group was 4.34%, 3 patients died from complications like recurrent optical glioma and cardiac arrest due to a cardiac neurofibroma. Complications less frequent (Jouhilahti EM. et al, 2011), not lethal, were partial hearing loss and the presence of prosthetic eye (fig.4).

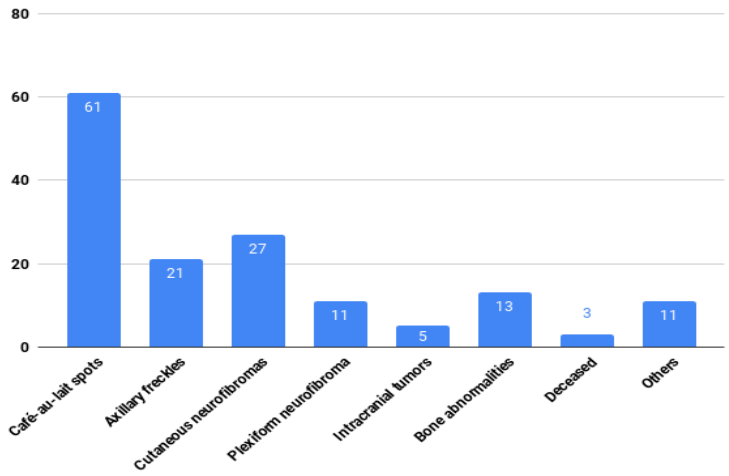

Fig.4. Evolution of neurofibromatosis : clinical signs, complications.

Cognitive deficits and learning disabilities are associated (Cohen R, Shuper A., 2010) with NF I in about 50% of the cases, generating social integration problems (Torres Nupan M.M., et al, 2017). In our study group

1/3 of the patients presented cognitive deficit, learning disabilities, could not follow their studies.

From the total number of patients, 13 had a disability degree and 3 had an invalidity pension. They had cognitive deficit, speech and language problems, had difficulties in their daily life. Both categories felt socially isolated and discriminated in their social group. NF I patients need psychological evaluation and advice (Garcia-Penas J.J. 2017);

All living patients from the study group, at working age, were employed in different fields, according to their training.

CONCLUSIONS

1. The variable expressivity of the neurofibromatosis type I is probably responsible for the late diagnosis of the patients with mild phenotype.

2. Patients with NF I needs annual evaluation, to prevent and treat in time any possible complication.

3. Genetic counseling is essential for adult patients in order to make family planning, especially considering the nowadays possibilities of prenatal molecular diagnosis.

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