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Case Report

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A Novel Mutation in Neurofibromatosis Type 1 with Optic Glioma

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Abstract: Neurofibromatosis type 1 is an autosomal dominant disorder which is characterized by multiple café-au-lait spots in the body, intertriginous freckles, Lisch nodules, neurofibroma, optic glioma and bone dysplasia. One of the clinical characteristics of Neurofibromatosis type 1 is the risk of benign and malignant tumor development. Optic gliomas, a type of astrocytoma, are the most common central nervous system complication in children with Neurofibromatosis type 1 and are seen in 10–15% of cases. In this case report, a patient with an optic glioma and a mutation that was not previously identified in the NF1 gene is presented in the light of the literature. Identification of new mutations that cause Neurofibromatosis type 1 disease and reporting of clinical findings caused by the mutations will allow a large proportion of genotype-phenotype correlation. Early diagnosis has a great importance in terms of follow-up of patients for malignancies that may develop in the future.

Keywords: Neurofibromatosis type 1; NF1 gene; novel mutation; optic glioma

1 Introduction

Neurofibromatosis type 1, also known as Von Recklinghausen disease, is an autosomal dominant disease with a prevalence of one case in 3,000 births. The disease is characterized by multiple café-au-lait spots in the body, intertriginous freckles, Lisch nodules, neurofibroma, optic glioma and bone dysplasia. Complications of the disease include malignant peripheral nerve tumors, neurocognitive disorders, epilepsy, and cardiovascular abnormalities [1]. The diagnostic criteria of Neurofibromatosis Type 1 according to the National Institute of Health includes: 1) Six or more cafe-au-lait spots with a diameter greater than 5 mm in pre-pubertal period and 15 mm in post-pubertal period, 2) At least 2 neurofibromas or one plexiform neurofibroma, 3) Axillary or inguinal region freckling, 4) Optic glioma, 5) Bone dysplasia (sphenoid dysplasia, pseudoarthrosis), 6) Positive family history of the disease in first degree relatives. The presence of two or more criteria is sufficient for the diagnosis of the disease [2].

Neurofibromatosis Type 1 disease is caused by a defect in the NF1 tumor suppressor gene localized in chromosome 17q11.2. The NF1 gene consists of a total of 60 exons that are developmental and tissue-specific, with at least 4 alternative splicing observed [3,4]. This gene encodes a 2818 amino acid protein carrying the functional GAP (GTPase-activating protein) in the central region, called neurofibromin [5]. Neurofibromine is expressed in different tissues containing neurons, especially in the central nervous system and astrocytes. Neurofibromine is involved in different cellular processes through signaling pathways. In particular, it promotes the conversion of ATP to cyclic AMP, resulting in a decrease in the level of c-AMP in the absence of NF1 gene activity. Through this pathway, neurofibromine has a positive effect on learning, survival and stress resistance in Drosophilia models [6]. In addition, neurofibromine exhibits GAP-like function and is a negative RAS regulator. Absence of neurofibromine, RAS activity is increased and MEK-ERK (MAPK, mitogen activated protein kinase) pathway and PI3K-Akt-mTOR pathway are induced. Through these pathways, neurofibromine plays a negative regulatory role in cell growth and proliferation [7,8].

The most common tumor in neurofibromatosis Type 1 is neurofibroma and usually has a benign course. Malignant tumors are rare in patients with Neurofibromatosis Type 1 and their distribution varies between populations. Half of the tumors develop in the central nervous system and these tumors are ependymoma, astocytoma, medullablastoma, meningioma, glioma. Optic gliomas are the most common intracranial tumor in patients with neurofibromatosis Type 1. In these patients, the risk of developing malignant tumors has increased, and the risk is about 16.3 times higher than the rate observed in the general population [9]. Almost all of the optic gliomas associated with NF1 appear as benign pilocytic astrocytomas. Optic gliomas are a NF1 perspective that is more prevalent in young children, further complicating diagnosis and accurate visual assessment in an at-risk population [10]. In this case report, a patient with an optic glioma and a mutation that was not previously identified in the NF1 gene is presented in the light of the literature.

2 Case Presentation

The patient was referred to the medical genetics outpatient clinic due to the presence of many cafe au lait spots on her body. Our patient was a 1-year-old female, the second child of a healthy and unrelated parents. The patient was born at term with spontaneous vaginal delivery. The birth weight was 3000 g (10–25p) and birth length was 50 cm (50–75p). In the physical examination; height 73 cm (25–50p), body weight 10 kg (50–75p), head circumference was determined as 45 cm (50–75p). Head development from the developmental stages was 3 months, walking 12 months. Numerous café-au-lait spots, the largest of which was 5 cm on the body, proptosis on the right eye, narrow and high palate, nasal root flattened, bulbous nose were detected in examination.

In hemogram, leukocyte was 11.7 × 10^3/μL, hemoglobin was 12.1 g/dL, hematocrit was 40.6%. Routine biochemistry, liver and thyroid function tests were normal. Abdominal and urinary system ultrasonography and echocardiography were normal.

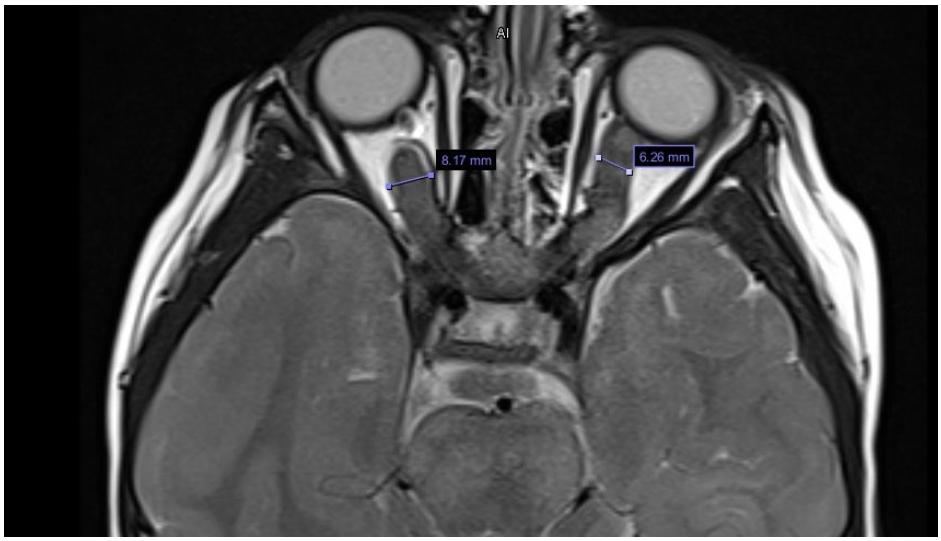

Figure 1: Orbita MR imaging of the patient showed optic nerve thickness was over 4 mm in the right and left eyes

In cranial magnetic resonance imaging, there were hyperintense lesions in the basal ganglia at the interna of the bilateral capsule, especially in the posterior part, at the globus pallidus and putamen level, at the bilateral medial temporal lobe level, in the mesencephalon and bilateral cerebellar hemisphere in T2A and FLAIR, and hypointense lesions in T1A. There was slight thinning in the corpus callosum. Orbital MRI showed thickening in bilateral optic nerve, optic chiasm and optic tract, more prominent on the right, elongation in some places, and pathological contrast material uptake in postcontrast series (Fig. 1).

In the genetic analysis of peripheral blood sample with the diagnosis of NF1 with clinical findings; 2.-57. exons were amplified by PCR method. Next generation sequencing analysis revealed that p. K1457* (c.4369 A>T) heterozygous mutation in exon 33 which was not previously described in the literature (Fig. 2a). The mutation was not previously defined in HGMD (Human Gene Mutation Database) and mutation taster bioinformatics program was assumed that this change was the cause of the disease. As a result of the mutation analysis performed on the mother and father of the case, the NF1 gene analysis of both was found to be normal (Figs. 2b, 2c). Also systemic examination was performed to the mother and the father of the patient and we observed that the parents had no clinical signs of neurofibromatosis. Cytogenetic investigation of the patient with a high-resolution-banded karyotype was also normal.

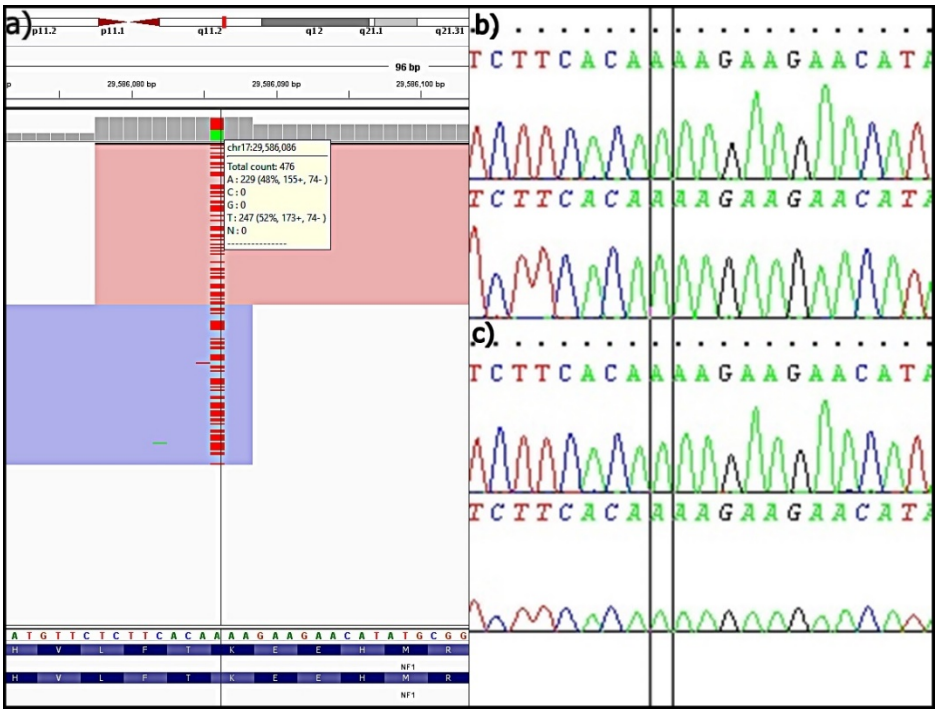

Figure 2: a) Next generation sequencing analysis revealed p. K1457* (c.4369 A>T) heterozygous mutation in exon 33, b) Sequence analysis of father of the case, c) Sequence analysis of mother of the case

3 Discussion

In this case report, a 1-year-old female patient with the diagnosis of neurofibromatosis Type 1 was described in the light of clinical and radiological findings and a new mutation in the NF1 gene was defined; p.K1457* (c.4369 A>T) as a result of molecular genetic analysis.

The mutation spectrum is complex and shows mutational heterogeneity due to the presence of multiple coding exons of the NF1 gene. Most of the mutations occur in 8 exons, which account for 16% of the coding region. Although most of the defined mutations are special, several hot spots with a higher mutation rate such as exons 4b, 7, 10b, 13, 15, 20, 29 and 37 have been described. Exon skipping mutations are mostly seen in exons 7, 29 and 30 [11,12]. Although NF1 is an autosomal dominant inheritance with 100% penetrance, major differences are observed between NF1 mutations and clinical presentations. Although the genotype-phenotype correlation of the disease has not been established yet, it is known that the clinical course is more severe, neurofibroma and malignant peripheral nerve tumor developments are more frequent only in microdeletions of NF1 gene. Also low IQ level and distinctive facial features are associated with microdeletions [1,13].

One of the clinical characteristics of Neurofibromatosis type 1 is the risk of benign and malignant tumor development. The most common tumors in NF1 are neurofibromas and develop from Schwann

cells. These benign tumors can also settle on or under the skin, or deep into the body. Neurofibromas are composed of nervous system and connective tissue. They can occur at any age, usually in adolescence, and do not spread rapidly. Superficial tumors are known as skin neurofibromas. Plexiform neurofibromas can spread to the lower surfaces of the skin or deep into the body. Observation of multiple neurofibromas on physical examination is important for the diagnosis of NF1 [14]. Neurofibromas are seen in 59.4% of the cases and while it is rare before puberty, its incidence increases with puberty [15]. Although plexiform neurofibromes are usually asymptomatic, they can reach very large sizes, cause pain, cause severe disfigurement, become overgrown, cause wear of surrounding tissues, or affect the function of nerves and other structures [16]. These benign tumors act as precursor lesions and can transform into malignant peripheral nerve sheath tumors (MPNSTs), with high body tumor burden being a strong risk factor for MPNST development. The risk of developing MPNST from neurofibromas in patients is 10%. Distant organ metastases usually develop and are the most common cause of death in NF1 patients [17].

The most common pathology observed in brain MRI in neurofibromatosis is hyperintense lesions seen in different localizations in T2A series. The characteristics of these lesions, called hamartoma, are that they are benign and they are not accompanied by neurological problems [18]. The formation of a melanocytic hamartoma in the iris is called the Lish nodule and is among the most common symptoms. On examination, small dome-shaped yellow-brown lesions are seen superficially in the iris with a slit lamp. It is one of the important criteria for diagnosis. They are usually detected in patients older than 6 years of age and do not cause visual impairment. The most common brain tumors in NF1 cases are optic gliomas. Optic gliomas, a type of astrocytoma, are the most common intracranial tumors in children with NF1. It may occur in 5–15% of patients and is one of the important causes of morbidity by causing complications in the central nervous system especially in young children with NF1. These tumors can settle in any part of the optic pathway. These lesions are mostly detected by MR imaging method. In NF1, optical gliomas are usually symptomatic in individuals younger than six years of age and occur with loss of visual acuity, proptosis or strabismus in patients, but may not become symptomatic if these tumors occur later in childhood or even adulthood [19,20]. In our case, optic glioma was detected, but no symptoms had occurred yet except proptosis. The patient had no additional complaints and a regression in thickening was detected in the second orbital MRI taken during her follow-up. We think that the patients being followed up by ophthalmology clinics due to early diagnosis has a great role in this.

Association of NF1 with optic glioma is not rare, but has occasionally been molecularly defined. Evidence from population-based clinical trials and preclinical studies using human induced pluripotent stem cells (iPSCs) and genetically modified mice revealed interesting genotype-phenotype correlations in NF1. It is possible that genotype is a significant determinant of the risk of development of the optic gliomas in NF1. In NF1 patients with optic gliomas, germline mutations appear to be localized from the 5'-end to the middle of the NF1 gene [21]. Further, human iPSCs derived from individuals with NF1 have been seen to have variable neurofibromine protein levels and function [22]. Specifically, mice with the Gly848Arg patient mutation do not form optic gliomas, while those harboring the Arg681X mutation develop larger volumes of optic gliomas and proliferative indices than those that occur in mice harboring the artificial knockout allele [23].

In this case report, p.K1457* (c.4369 A>T) heterozygous mutation which was not previously described in literature was detected in exon 33 as a result of NF1 gene molecular analysis. Molecular analysis was performed for the parents to guide genetic counseling in subsequent pregnancies. It was observed that the mutation analysis result of the mother and father was normal and the mutation was de novo. It is known that 30–50% of neurofibromatosis Type 1 cases develop as a result of spontaneous mutation. Recommendations for the evaluation of parents of a proband with a de novo pathogenic mutation include medical history and physical examination with particular attention to features of NF1. Systemic examination was performed to the parents and it was observed that the they had no signs of neurofibromatosis. It should be borne in mind that germline mosaicism is possible but much less likely in a parent without clinical signs of NF1.

Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible if the pathogenic variant in a family is known. Once the NF1 pathogenic mutation has been identified in an affected family member, prenatal testing [24] for a pregnancy at increased risk and preimplantation genetic testing [25] are possible. While counseling in terms of prenatal diagnosis, information about variable expressivity and phenotypic difference should be given to the family. Since the severity and age of onset of the disease are very variable, the decision for prenatal diagnosis should be made by the family after detailed genetic counseling. At this point, preimplantation genetic diagnosis may be an important option [26]. Although the possibility of developing the disease in future pregnancies is low due to the absence of mutation carriers in parents, the family was informed about the risk of developing the disease in future pregnancies and genetic counseling was given to the family. Also our patient is followed up for any pathologies, complications and malignancies that might accompany in the future.

4 Conclusion

In conclusion, identification of new mutations that cause Neurofibromatosis Type 1 disease and reporting of clinical findings caused by the mutations will allow a large proportion of genotype-phenotype correlation. Reporting the clinical findings observed in patients with the same mutation will create a pool in the databases in the future and guide clinicians about the management. On the other hand, early diagnosis is of great importance in terms of follow-up of patients for malignancies that may develop in the future.

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