Int J Clin Exp Pathol 2020;13(10):2656-2660
www.ijcep.com /ISSN:1936-2625/IJCEP0119042

Case Report

Neurofibromatosis type I in children: a case report and literature review

Jing Wang*, Yaqian Pang*, Feng Cao, Hao Zhu, Kai Zhang*

*Department of Stomatology, The First Affiliated Hospital of Bengbu Medical College, Bengbu 233004, Anhui, P. R. China. *Equal contributors.*

Received July 27, 2020; Accepted September 14, 2020; Epub October 1, 2020; Published October 15, 2020

Abstract: Neurofibromatosis is an autosomal dominant genetic disease that originates from neuroepithelial tissue and involves disorders of ectoderm and mesoderm. At present, there are relatively few reports of neurofibroma type I in children. Therefore, understanding the clinical manifestations, diagnosis, and treatment of neurofibromatosis is of great significance to the occurrence and development of neurofibroma type I. This study is a case of and literature review of neurofibromatosis type I in children.

Keywords: Neurofibromatosis, autosomal dominant hereditary disease, literature review

Introduction

Neurofibromatosis (NF) is a rare progressive disease, usually caused by mutations in a specific gene. NF is mainly divided into three types, and type I (NF1) and type II (NF2) are most common [1, 2]. The incidence of NF1 is approximately 1/3,000 to 1/400, accounting for about 85% of neurofibromatosis. The disease commonly begins at a young age in children and involves multiple systems such as nervous, endocrine, circulatory and urinary systems, as well as bone and mental development. About 25%~50% of patients with NF1 have a positive family history, which is characterized by multiple cutaneous neurofibroma and skin milk coffee spots [3]. NF1 sporadically involves maxilla, temporal bone, zygomatic arch, temporomandibular joint, parotid gland, and external auditory canal. The incidence of NF2 is about 1/50,000, and it is commonly accompanied by bilateral acoustic neuroma. Since the incidence of NF1 is dozens of times higher than that of NF2, more attention and research has been focused on NF1.

Case report

The patient, male, eight years old, was admitted to hospital because of "left facial mass for more than half a year". Six months ago, the family members of the patient inadvertently found a "soybean" painless, hard mass on the left face of the child. After seeing a doctor in the local hospital, the patient was treated with anti-inflammatory treatment (specific drugs are unknown). The effect was poor, and the mass gradually increased. The family members of the children came to our hospital for further treatment, and patient was admitted to the hospital with "left facial mass". Physical examination: the general condition was good, the vital signs were stable, no abnormal symptoms were examined in the heart, lung, abdomen and nervous system, and the superficial lymph nodes of the whole body were not touched. A "3 cm × 2 cm × 2 cm" mass was palpable in the left parotid gland, with hard quality, reduced range of motion, and tenderness (+). There was no redness and swelling at the mouth of the left parotid duct, and the secretion was clear. A large number of scattered café au lait spots were seen in the neck, upper body, and armpits (**Figure 1A**). After improving the relevant examinations and excluding surgical problems, "partial resection of left parotid gland + partial parotidectomy + facial nerve dissection" was performed under general anesthesia. During the operation, there was a cord-like neurofibroid lesion outside the parotid capsule

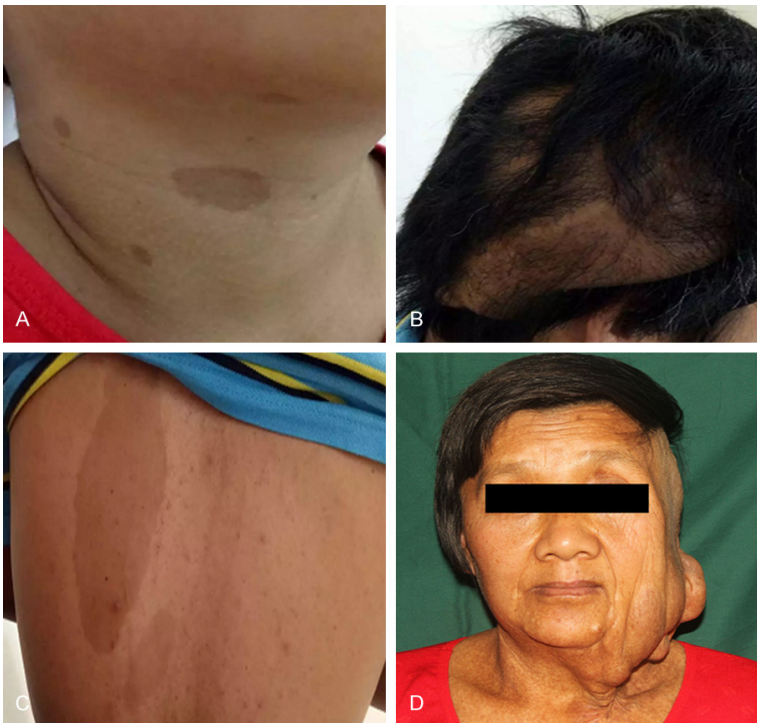

Figure 1. Clinical manifestations of the patient and his families: A. Café au lait spot on neck. B. Head lump. C. Café au lait spots on the back. D. Giant tumor in left face and neck with drooping deformity.

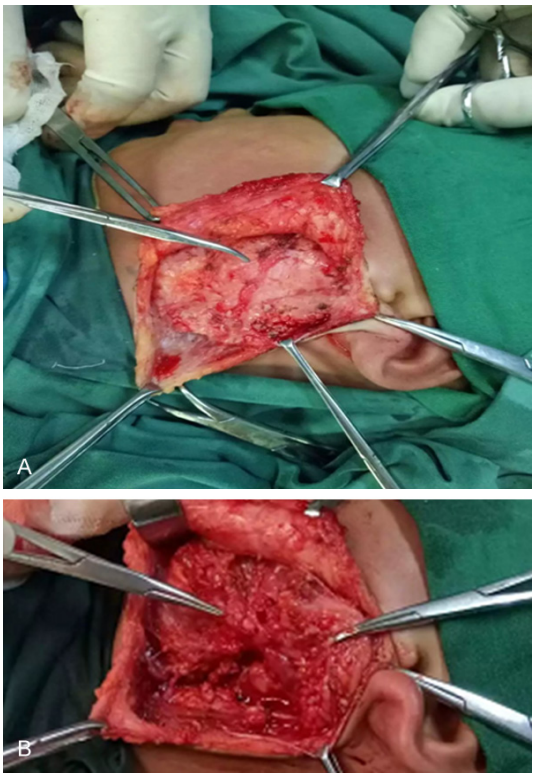

Figure 2. Intraoperative situation: A. Cord-like neurofibroid disease. B. The facial nerve is like a string of beads.

(**Figure 2A**). After opening the parotid capsule, the meeting nerve was beaded, the cervicofacial trunk was thick (**Figure 2B**), the facial nerve function was preserved, and the tumor was partially resected. Postoperative pathology (**Figure 3**) showed: (left maxillofacial) parotid gland tissue and fibroadipose tissue, local nerve, and adipose tissue hyperplasia. Another two lymph nodes showed reactive hyperplasia. Therefore, the disease was diagnosed as "left facial neurofibromatosis". The basic information and tissue specimens of the patients involved in this study were approved by the hospital ethics committee, and the patients were informed and agreed.

Discussion

NF1 progresses slowly and it can occur in both infancy and adolescence. The symptoms in adolescence and pregnancy are apparent. Incidence during adolescence may be related to the relative increase of gene mutation and expression error, and incidence during pregnancy may be related to the changes in hormones in the body. The NF1 gene is located in the 17q11.2 region and contains 57 exons and 4 alternative splicing exons. About 50% of the patients have inherited NF1 gene mutations, and the rest are caused by mutations in the NF1 gene. The spontaneous mutation rate of the NF1 gene is up to 1/10,000, which is one of the highest known mutation rates in human genes. There are more than 500 known mutation sites, which brings significant challenges to the study of the relationship between genotype and phenotype [4]. NF1 gene mutations include the following types: chromosome aberration, multiple exon deletions or large insertions, termination mutations, amino acid substitution, intron mutations, and 3' untranslated region mutations. The clinical manifestations of gene deletion, insertion, or mutation mainly occur in the tongue (26%), buccal mucosa (8%), lip mucosa (8%), taste buds (8%), gingiva (2%), and the most common place is the papillae of the

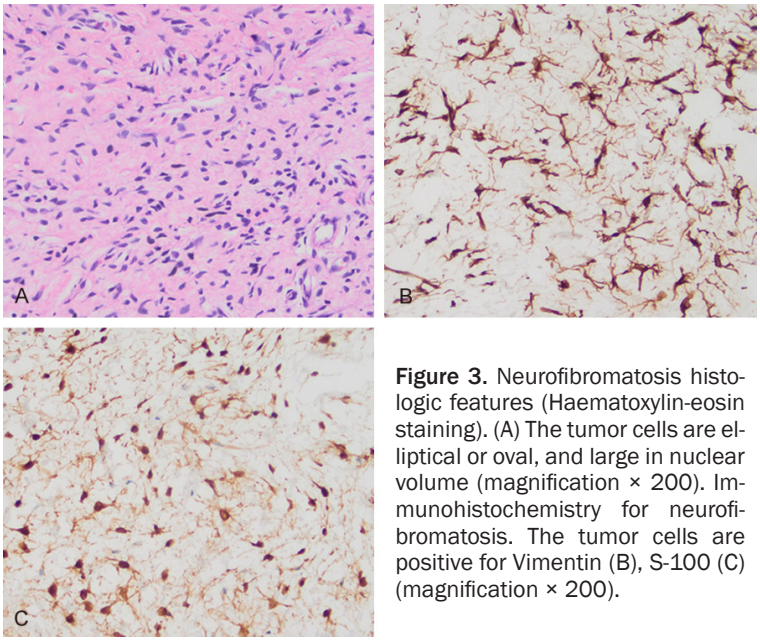

Figure 3. Neurofibromatosis histologic features (Haematoxylin-eosin staining). (A) The tumor cells are elliptical or oval, and large in nuclear volume (magnification × 200). Immunohistochemistry for neurofibromatosis. The tumor cells are positive for Vimentin (B), S-100 (C) (magnification × 200).

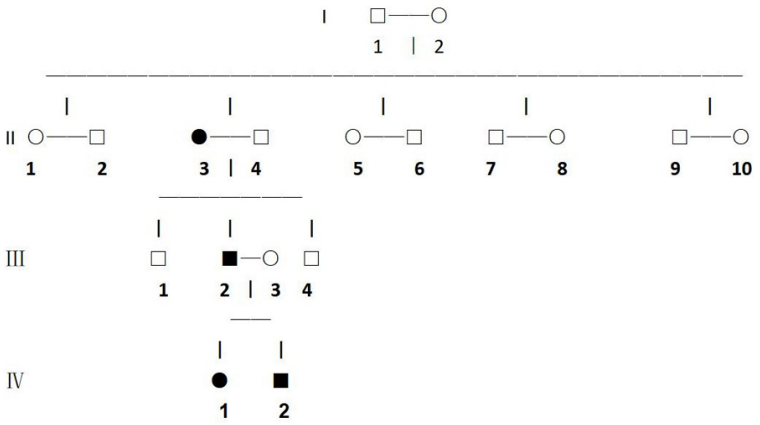

Figure 4. The genealogical tree. The reported case (IV 2), his father (III 2), younger sister (IV 1), and grandmother (II 3).

tongue [5]. Previous studies indicated that base substitution mutations often occur when mutations occurred on the chromosomes of patrilineal origin, and deletions often occur on the chromosomes of matrilineal origin [6]. In this study, the child (IV 2) had an obvious family history, and his father (III 2), younger sister (IV 1), and grandmother (II 3) all suffered from neurofibromatosis. The scattered freckles, café au lait spots and multiple subcutaneous nodules could be seen on the whole body of patient's father (**Figure 1B**). A 5.0 cm × 15.0 cm × 3.0 cm mass was seen on the right side of the head, with a soft texture, clear boundary, reduced range of motion and tenderness (-) (**Figure 1C**). Her grandmother had scattered freckles, café au lait spots and multiple subcutaneous nodules all over her body (**Figure 1D**). His sister's whole body presented with scattered freckles, and café au lait spots. Family investigation results demonstrated that (**Figure 4**) there were 4 cases of the disease in 18 people in 4 generations, II 3 was gene mutation, III 2, IV 2 and IV 1 were hereditary, IV 2 and IV 1 were dizygotic twins. The pedigree map showed that there were patients in each generation in accordance with the law of euchromatic inheritance.

NF2 is relatively rare, accounting for less than 10% of neurofibromatosis, with an incidence of 1/50,000. It is an autosomal 22 long arm gene defect [7], with little or no skin pigmentation with meningioma, cranial schwannoma, and spinal cord schwannoma. Its clinical diagnostic criteria: (1) first-degree relatives have bilateral acoustic neuroma; (2) the patient suffers from this disease plus unilateral acoustic neuroma or has 2 of the following kinds of tumors such as Schwann's cell tumor, neurofibroma, meningioma, glioma [8, 9].

According to the NF1 diagnostic criteria proposed by the National Institutes of Health in 1988, at least two criteria must be met: (1) ≥ 6 milk coffee spots with the maximum diameter > 5 mm before puberty and > 15 mm after puberty; (2) ≥ 2 neurofibromas of any type or one plexiform neurofibroma; (3) axillary freckles; (4) optic gliomas ≥ 2 Lish nodules; (5) characteristic bone damage, such as sphenoid dysplasia, thinning of long bone cortex or pseudarthrosis; (6) first-degree relatives with NF1. The incidence of optic glioma, Lish nodules, and characteristic bone damage is low. Café au lait spots are the earliest clinical manifestations of NF1. 99% of NF1 patients appear

before 1 year old, and 90% of adult NF1 patients have axillary freckles [10-13]. This patient met 3 criteria and can be diagnosed with left facial neurofibromatosis. The facial nerve includes five groups of branches in the parotid gland, and most neurofibromas originate from parotid gland, especially plexiform neurofibroma [14].

Neurofibromatosis of the head and neck is a benign tumor that is difficult to treat. The recurrence rate of some tumors is high and the cure rate is low. For localized and beaded cases, complete resection and preservation of nerve continuity are the first treatment choice. For invasive and diffuse patients, the tumor can only be removed as much as possible. If the motor nerve is involved, it is necessary to choose between the complete resection of the tumor and the protection of nerve function. Current surgical methods attempt to achieve both. The recurrence rate of plexiform neurofibroma is high, and the malignant transformation rate is about 10% higher than other types of neurofibroma [15]. Follow-up should be paid attention to in the clinic. The possibility of malignant transformation or infection should be considered when neurofibroma overgrows. The malignant transformation rate is about 3-14%, and the incubation period is about 10-20 years [16]. At present, there is no effective measure to prevent or reverse the course of NF1, so symptomatic treatment is the only option [17]. The tissue of NF1 tumor is fragile and tender, and many blood vessels with thin walls and poor elasticity exist in the tumor, making it difficult to stop bleeding during operation [18, 19]. The commonly used hemostatic methods during the operation are: (1) resection in the healthy tissue around the tumor, avoiding the blood sinus in the mass, ligation and then amputation during the operation; (2) if the tumor is located in the extremities, a tourniquet can be used to remove the tumor without blood, and if the tumor is located in the neck, the external carotid artery can be ligated first; (3) intraoperative use of antihypertensive drugs can reduce intraoperative bleeding, between 8.0 and 10.6 kPa, and the time should not exceed 30-45 minutes; (4) segmented tumors can be resected by stages and segments; (5) the tumor is ligated with No. 7 silk thread, and the line crosses with the line to reduce the blood supply of the tumor.

In summary, prenatal diagnosis and gene therapy at the genetic level are of great significance. Fetal DNA extracted from chorionic or amniocentesis can be used for direct prenatal mutation detection. However, many people are reluctant to accept this prenatal assessment because it is impossible to determine the severity of the disease. Preimplantation genetic diagnosis (PGD) [20] has been used in hereditary tumor susceptible patients with tumor suppressor gene mutations, and successfully predicted the later stage of tumor occurrence in susceptible patients. This proved that the PGD technique is an effective method to prevent the birth of babies with genetic tendency toward NF1 and NF2.

Conclusion

In summary, Neurofibromatosis of the head and neck is a benign tumor that is difficult to cure. The recurrence rate of some tumors is high, and the cure rate is low, which impact on the facial morphology and function of the patients. At present, the treatment of this disease is mainly partial or complete resection of the tumor. The aim of this report is to call on pregnant women to actively carry out preoperative diagnosis and gene therapy in order to reduce the incidence of such diseases. Patients should be followed up regularly after the operation to prevent malignant transformation or recurrence of the disease. In some cases, patients should be followed up for a longer time to guide patient care and predict outcome.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Kai Zhang, Department of Stomatology, The First Affiliated Hospital of Bengbu Medical College, Bengbu 233004, Anhui, P. R. China. Tel: +86-0552-3086336; Fax: +86-0552-3086336; E-mail: zk29788@163.com

References

[1] Yohay KH. The genetic and molecular pathogenesis of NF1 and NF2. Semin Pediatr Neurol 2006; 13: 21-26.

[2] Widemann BC, Acosta MT, Ammoun S, Belzberg AJ, Bernards A, Blakeley J, Bretscher A, Cichowski K, Clapp DW, Dombi E, Evans GD, Ferner R, Fernandez-Valle C, Fisher MJ, Giovan-

nini M, Gutmann DH, Hanemann CO, Hennigan R, Huson S, Ingram D, Kissil J, Korf BR, Legius E, Packer RJ, McClatchey AI, McCormick F, North K, Pehrsson M, Plotkin SR, Ramesh V, Ratner N, Schirmer S, Sherman L, Schorry E, Stevenson D, Stewart DR, Ullrich N, Bakker AC and Morrison H. CTF meeting 2012: translation of the basic understanding of the biology and genetics of NF1, NF2, and schwannomatosis toward the development of effective therapies. Am J Med Genet A 2014; 164A: 563-578.

[3] Zhao ZW, Sun CF, Li J, Feng J, Jiang L, Li XY and Li YJ. Application of plastic surgery in the surgical treatment of type I giant neurofibromatosis. J Pract Med 2018; 34: 166-168.

[4] Korf BR. Neurofibromatosis. Handb Clin Neurol 2013; 111: 333-340.

[5] M S, Joseph B, Nath SG and Sheejith B. An unusual case of multiple intraoral manifestations of neurofibromatosis type 1: case report with literature review. J Clin Diagn Res 2014; 8: ZD20-22.

[6] Wu-Chou YH, Hung TC, Lin YT, Cheng HW, Lin JL, Lin CH, Yu CC, Chen KT, Yeh TH and Chen YR. Genetic diagnosis of neurofibromatosis type 1: targeted next- generation sequencing with Multiple Ligation-Dependent Probe Amplification analysis. J Biomed Sci 2018; 25: 72.

[7] Parry DM, Eldridge R, Kaiser-Kupfer MI, Bouzas EA, Pikus A and Patronas N. Neurofibromatosis 2 (NF2): clinical characteristics of 63 affected individuals and clinical evidence for heterogeneity. Am J Med Genet 1994; 52: 450-461.

[8] Gaudioso C, Listernick R, Fisher MJ, Campen CJ, Paz A and Gutmann DH. Neurofibromatosis 2 in children presenting during the first decade of life. Neurology 2019; 93: e964-e967.

[9] Coy S, Rashid R, Stemmer-Rachamimov A and Santagata S. An update on the CNS manifestations of neurofibromatosis type 2. Acta Neuropathol 2020; 139: 643-665.

[10] Lozano-Masdemont B, Franco-Muñoz M and Sanz-Trenado JL. Segmental neurofibromatosis in the face. Med Clin (Barc) 2016; 147: e35.

[11] Santos Alarcón S, García-Briz MI and Mateu-Puchades A. Comorbidity associated to segmental neurofibromatosis. Med Clin (Barc) 2019; 152: 33.

[12] Korf BR. Spinal neurofibromatosis and phenotypic heterogeneity in NF1. Clin Genet 2015; 87: 399-400.

[13] Antônio JR, Goloni-Bertollo EM and Trídico LA. Neurofibromatosis: chronological history and current issues. An Bras Dermatol 2013; 88: 329-343.

[14] Seymour-Dempsey K and Andrassy RJ. Neurofibromatosis: implications for the general surgeon. J Am Coll Surg 2012; 195: 553-563.

[15] Upadhyaya M, Han S, Consoli C, Majounie E, Horan M, Thomas NS, Potts C, Griffiths S, Ruggieri M, von Deimling A and Cooper DN. Characterization of the somatic mutational spectrum of the neurofibromatosis type 1 (NF1) gene in neurofibromatosis patients with benign and malignant tumors. Hum Mutat 2004; 23: 134-146.

[16] Coffin CM, Cassity J, Viskochil D, Randall RL and Albritton K. Non-neurogenic sarcomas in four children and young adults with neurofibromatosis type 1. Am J Med Genet A 2004; 127A: 40-43.

[17] Sun SL, Wang ZF, Ma JL, Zhu GD, Ding L and Wang WJ. Surgical treatment of head and neck giant neurofibromatosis: report of three cases. J Oral Maxillofac Surg 2018; 28: 85-89.

[18] De Santis F, Negri G, Martini G and Mazzoleni G. Multiple aneurysms of the radial artery in a woman with neurofibromatosis type 1 presenting as aneurysm rupture. J Vasc Surg 2013; 58: 1394-1397.

[19] Claeys MA and Gepts E. Haemodynamic changes during anaethesia induced and maintained with propofol. Br J Anaesth 2012; 60: 3-9.

[20] Sullivan-Pyke C and Dokras A. Preimplantation genetic screening and preimplantation genetic diagnosis. Obstet Gynecol Clin North Am 2018; 45: 113-125.