Oral findings in 50 children with neurofibromatosis type 1. A case control study

ABSTRACT

Alm The scientific literature is poor of data concerning NF1-related oral manifestations in children. The purpose of this study was to investigate the oral findings in a group of children with NF1.

Materials and methods This study was designed as a clinical research. A total of 50 children affected by NF1 were enrolled. Non-NF1 controls were selected among subjects referred to the Paediatric Dentistry Department of the Dental Clinic at the University of Brescia, Italy. The craniofacial and all the dental examinations were carried out. The following parameters were investigated: dental caries, dental abnormalities, periodontal status, oral and perioral neurofibromas, orthodontic features, mandible and temporomandibular joint abnormalities. Statistics Unpaired Student's t test was calculated for Gaussian distributed variables; Fisher's test for non-Gaussian distributed variables was used. The values inferior to p<0.05 (threshold) were considered significant for the study.

Results Children with NF1 showed poorer oral hygiene conditions, more frequent Class III dental malocclusions and severe alterations of the mandible and the temporal mandibular joint, if compared with the control group.

Conclusion NF1 related-oral manifestations are evidenced also during childhood, even if some of the best known, like the neurofibromas, are not yet developed. It is important to keep a long-term follow-up to monitor the possible development of other oral lesions.

Keywords: Genetic disorders; Malocclusions; Neurofibromas; Oral cavity.

Introduction

The disease known as neurofibromatosis (NF) is now recognized as a group of genetic disorders that primarily affect the cell growth of neural tissues. Two forms of NF are generally accepted: neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2). These two forms of NF have few common features and they are caused by mutations of different genes; recent discoveries in molecular genetics have produced a sharp delineation between the two variants of NF [Cuhna et al., 2004].

NF1, also referred as von Recklinghausen's disease, is the most common type of NF and accounts for about the 90% of the cases. It is one of the most frequent human genetic diseases with a prevalence of one case every 3000 births. There is no gender or race predilection. The expressivity of the disease is extremely variable, with manifestations ranging from mild lesions to several complications and functional impairment. The penetration, otherwise, is 100%. Neurofibromas constitute an important feature of NF1. Café-au-lait spots, axillary and inguinal freckling, optic glioma, Lisch nodules (pigmented hamartomas of the iris) and specific bone lesions are also common clinical features of NF1. Oral manifestations can be found in almost 72% of NF1 patients [Geist et al., 1992].

Oral manifestations of NF include dental abnormalities such as impacted, displaced, supernumerary or missing teeth, bone abnormalities such as intrabony neurofibromas, hypoplasia and deformity of the jaw, enlarged mandibular foramen, flat or missing gonial angle, coronoid notch deformity, pseudoelongation of the condylar processes and soft tissues abnormalities such as oral neurofibromas. The characteristic clinical features of NF1 are usually visible during childhood or in the early adolescence. Since NF1 is a slowly worsening disease, it is important to identify as soon as possible the early oral signs. Literature is poor of data regarding the oral findings in children with NF1, in particular about which kind of oral manifestations are more common at this age [Geist et al., 1992].

The aim of this study was to analyse a group of children with NF1 in order to investigate the oral findings.

Materials and methods

Sample selection

This study was designed as a clinical research. Cases were identified as patients affected by NF1 diagnosed in the Neuropsychiatric Department of the Paediatric Clinic of Brescia and studied over a period of 18 months (from September 1st, 2008 until February 28, 2010).

Fifty-five children affected by NF1 (21 females and 34 males, mean age 7.83 and SD 3.04 years), attending the Children Neuropsychiatric Department were enrolled in the study. Five patients were excluded from the study: two cases because parents did not sign the informed consent, two cases because it was impossible to perform the visit as they were uncooperative and one case because the parents refused the orthopantomographs.

A total of 50 healthy children (31 males and 19 females) matched to cases for age, race and area of residence were enrolled. Non-NF1 controls were sequentially selected among subjects referred to the Paediatric Dentistry Department of the Dental Clinic at
NF1 was diagnosed according to the criteria outlined by the National Institutes of Health Consensus Development Conference [N.I.H.C.D.C, 1988]. Medical and dental history for each child were collected.

Methods
After obtaining written informed consent from the children parents, the patients were examined in the Department of Paediatric Dentistry, University of Brescia, Italy. The craniofacial and all dental examinations were carried out between the years 2008-2010 by the same two clinicians who had previously undergone calibration to standardize their procedures. The following parameters were investigated:

• Dental caries
  Caries were searched using a sharp explorer, fiber optic transillumination and mouth mirror. According to the WHO criteria (1979), caries were recorded as decayed (D), missing (M) and filled (F) teeth (T) resulting in DMFT index for the permanent teeth and as decayed (d), extracted (e) and filled (f) teeth (t) for the deciduous teeth (deft) [Visnapuu et al., 2011].

• Dental abnormalities
  The dental abnormalities were evaluated both clinically and radiographically. Orthopantomographs were performed for each patient. Each alteration of number, development and shape was registered and photographed.

• Periodontal status
  - Clinical assessment of the oral hygiene status was performed with a mouth mirror and explorer, using the criteria of the simplified oral hygiene index (OHI-s) by Green and Vermillion [1964].
  - The CPI (Community Periodontal Index) was used to describe the gingival health conditions. The conditions included CPI-scores 0 (healthy) and 1 (bleeding). As recommended by the WHO, periodontal pockets were not recorded, because the population of this study was under the age of 15 years [World Health Organization, 1997]. Inspection was carried out with a plan mirror and explorer.

• Oral and perioral neurofibromas
  Intra and perioral examination and palpation of soft tissues were performed to investigate the presence of nodules.

• Orthodontic features
  Cephalometric studies were not performed. The assessment of the dental occlusion was performed using dental mouth mirrors and millimetric rulers. The following orthodontic variables were considered.
  - Molar relationship. The relationship between the upper and lower first permanent molars was determined according to Angle’s classification. Patients with subdivision malocclusions were included in the Class II or Class III groups on the basis of the predominant characteristics or according to the relationship between the canines.
  - Posterior cross bite. A posterior cross bite was diagnosed when there was a crossover of at least one tooth in the posterior segment of the dental arches. The posterior cross bite could be unilateral (right or left) or bilateral.
  - Scissor bite. A scissor bite was considered to be present when the palatal cusps of the upper molars were positioned buccally in relation to the buccal cusps of the lower molars.
  - Crowding and diastemas. These characteristics were recorded for the anterior and the posterior segments as well. A midline diastema was recorded when there was a space of at least 2 mm between the maxillary central incisors.

• Mandible and temporomandibular joint (TMJ) abnormalities
  Orthopantomographs were taken for each patient to point out specific radiographic characteristics of NF i.e. intrabony neurofibromas, hypoplasia and deformity of the jaw, widening and branching of the mandibular canal, flat or missing gonial angle, coronoid notch deformity, pseudoeelongation of the condylar processes.

Data analysis
Initially, clinical condition parameters were assessed by means of univariate analysis to describe the variables and distributions. Unpaired Student’s t test between the two groups was calculated for Gaussian distributed variables; Fisher’s test for non-Gaussian distributed binomial variables was used. Values lower than p<0.05 (threshold) were considered significant.
Results and discussion

A total of 100 patients were examined. Table 1 shows the oral findings in patients with NF1 and in the control group. Despite the advances of molecular biology, the diagnosis of NF1 and NF2 is still based on clinical criteria. The National Institute of Health Consensus Development Conference originally established in 1988 the diagnostic criteria for NF1 and NF2 [Stumpf et al., 1988].

In the past, the frequency of oral manifestations of NF1 was estimated to occur from 4 to 7% of the cases [Neville et al., 1995]. Afterwards, many studies suggested that the oral manifestations are much higher [D’Ambrosio et al., 1988; Shapiro et al., 1984].

The low frequency of oral manifestations in certain studies can be explained by the lack of radiographic examinations, ignoring the intraosseus manifestations. In fact, in a study performed by Shapiro et al. [1984], oral manifestations were radiographically identified in 72% of the patients with NF1; according to a survey performed by D’Ambrosio [1988] 66% of NF1 patients had at least one intraoral manifestation of the disease and 58% of the patients presented manifestations in the maxilla and the mandible, detected with the panoramic radiographs. In a study conducted by Friedrich et al., oral involvement is reported to occur in 3.4-92% of adult patients with NF1 [Friedrich et al., 2003].

Whereas the oral findings in NF1 adult patients have been the topic of a great number of surveys, there are very few investigations that have evaluated the rate and type of oral manifestations during childhood.

The purpose of this study was to investigate the oral findings in a group of children with NF1 and to compare them with a matched group of healthy children. We considered six criteria: dental caries, dental abnormalities, periodontal status, oral and perioral neurofibromas, orthodontic features, jaw bone and TMJ.

Dental caries

The rate of dental caries in NF1 children is still quite controversial.

In a recent study performed by Visnapuu et al. [2011] on a large cohort of 110 NF1 patients, they found that an increased number of caries is not a typical feature in NF1. In particular, the 50 NF1 patients from 3 to 20 years of age included in the study showed a cumulative prevalence value (DMFT>0) lower than in the control group, probably due to major attention of the parents in assisting the children during the oral hygiene.

On the contrary, a previous study reported increased dental caries in people with NF1 in Canada [Tucker T et al., 2007]. In this study, questionnaires regarding dental caries were given to the families that included at least one individual with NF1. Siblings with NF1 reported significantly more dental caries than siblings without NF1 in these families. They supported their findings on the basis of a study of Lammert et al., where they observed that individuals with NF1 have a lower mean serum 25-hydroxyvitamin D3 (vitamin D) concentration than individuals without NF1 [Lammert et al., 2006]. However, the data of this study derived from a questionnaire and not from a direct clinical examination of the patients. A later Canadian study [Tsang et al., 2010] examined 18 children with NF1 and their unaffected siblings, finding a similar prevalence of caries in the affected subjects and their unaffected sibs. According to these last results, we did not find any significant statistical difference between dmft/DMFT in children with NF1 vs. healthy children.

Dental abnormalities

Dental abnormalities are reported to occur in patients with NF1 [Friedrich et al., 2003]. However, in the studies performed on adults, these malformations are strongly associated with plexiform neurofibromas originating from the trigeminal nerve. In our children with NF1, we did not find any tumor of the jaws, so the reported dental abnormalities are to be considered primitive.

Regarding the number of patients with dental abnormalities, we did not find any significant difference between the children affected by NF1 (13/50) and the control group (7/50).

| TABLE 1 - Oral findings in children with NF1 and in the control group. NS = not significant,*p<0.05,**p<0.01 sd=standard deviation |
|-----------------|-----------------|-----------------|-----------------|
|                  | NF1 (50)        | control (50)    | significance    |
| **Dental caries**| Mean dmft/DMFT +sd | 1.82+_1.69 | 1.30+_1.59 | NS |
| **Dental abnormalities** | N. patients with abnormalities | 13 | 7 | NS |
| **Periodontal status** | CPI | NS |
| Healthy (0) | n=21(42%) | n=27(54%) |  |
| Bleeding (1) | n=29 (58%) | n=23 (46%) |  |
| OHI-s mean + sd | 1.426+1.274 | 0.884+1.126 |  * |
| **Oral and perioral neurofibromas** | N. patients with neurofibromas | 0 | 0 | NS |
| **Orthodontic features** | Dental Class I | n=29 | n=31 |  NS |
| Dental Class II | n=10 | n=16 | NS |
| Dental Class III | n=11 | n=3 | * |
| Posterior crossbite | n=9 | n=7 | NS |
| Scissor | n=0 | n=0 | NS |
| Crowding and diastema | n=26 | n=22 | NS |
| **Jaw bone and TMJ abnormalities** | N. patients with abnormalities | n=14 | n=0 | ** |
|
Among the children with NF1, we found 6 patients with taurodontic teeth, 4 with agenesis and 3 with enamel hypoplasia while among the control group we found 2 patients with agenesis and 5 with enamel hypoplasia. From our data, taurodontism is confirmed to be the most frequent dental abnormality in children with NF1, having a significant statistical difference (p=0.027) with the control group.

**Periodontal status**

Literature based on the oral health status in children with NF1 is scarce. Even if there are studies about gingival features in these children, these are focused on the research of neurofibromas and they do not assess the oral hygiene status. In this study we evaluated the oral hygiene status and the gingival health conditions. We found a significant difference (p=0.02) between the mean of the OHI-s in children with NF1 (1.426+1.274) and the mean of the OHI-s control group. (0.884+1.126); on the contrary, with the CPI we did not find any significant difference (p>0.05) between the gingival bleeding in children with NF1 (58%) and the control group (46%).

From our results, it seems that even if the oral hygiene conditions are lower in children with NF1, the gingival health conditions are similar to those in healthy children. However, the maintenance of a poor oral hygiene may contribute in the progression of periodontal disease in adults affected by NF1.

**Oral and perioral neurofibromas**

Oral localised neurofibromas appear like discrete nodules of normal color and they are usually asymptomatic. The majority of oral neurofibromas occur in the tongue. In fact, the most common oral lesion of NF1 affecting the mucosa, reported in literature, is the enlargement of the fungiform papillae of the tongue that occurs in about the 50% of the cases; Shapiro et al. observed gingival neurofibromas in only the 5% of all the patients affected with NF1 [Shapiro et al., 1984; Vincent et al., 1983]. Nevertheless, neurofibromas on or adjacent to the cranial nerves also affect the motor function of the facial and hypoglossal nerves and the sensory function of the trigeminal nerve [Cuhna et al.,2004; Shapiro et al., 1984].

No data are currently available about neurofibromas in children affected by NF1. All the children enrolled in the study were examined to investigate the presence of nodules in the soft tissues. We did not observe neurofibromas neither in the children affected by NF1 nor in the control group. Our data show that oral neurofibromas are not manifestations occurring in childhood.

**Orthodontic features**

While epidemiological data about orthodontic features in healthy children are widely available, there is a lack of surveys about the prevalence of malocclusions in children with NF. This study examined the occlusal conditions of orthodontically untreated children. The following orthodontic variables were evaluated: molar relationship, posterior cross bite, scissor bite, crowding and diastemas. We did not find any significant difference between children with NF1 and the control group, except for the molars relationship. In fact, we found a significant difference (p=0.041, RR=3.667) between the prevalence of Class III malocclusion in healthy children (6%) and in children with neurofibromatosis (22%). These findings suggest the need of early orthodontic screening for Class III malocclusion in children with NF1.

**Mandible and TMJ abnormalities**

There are few studies about radiographic features of the jaws in children with NF and they report three basic types of involvement. The first is the central bony lesion that is considered to be rare in NF; the second is the erosion of the external surface of the bone for the presence of adjacent soft tissue lesions; the third is a bone deformity similar to the dysplasia [Lee,1996; Kaplan et al, 1994; Holtzman,1998; Lorson et al., 1977; Müller and Sloatweg, 1981].

About this last type, Lorson [1977] felt that the change of the shape of the coronoid notch was a pathognomonic feature and was as important as the characteristic sphenoid and orbital dysplasia to NF. Also Müller and Sloatweg [1981] stated that the skeletal lesions might be pathognomonic. Lee et al. [1996] supported the theory that neurofibromatosis may have manifestations of a mesodermal dysplasia, well describing 10 cases of NF with patients ranging from 6 to 20 years of age.

Mandible may be affected by these alterations, as it is a long bone. The characteristic sites of NF1-associated osseous manifestations are the long bones (usually the tibia and fibula), vertebrae and sphenoid wing. Alwan et al. [2007] suggested that some individuals with NF1 are more prone to develop osseous manifestations than others and speculated that there may be a common pathogenetic mechanism responsible for the development of osseous abnormalities of the vertebrae and long bones.

In our study, out of 50 children with NF1, 14 (28%) patients showed radiographic features of NF. Eighteen children (36%) showed increase in dimension of the coronoid notch and deformity of the condylar head; increase in bone density and enlarged mandible foramen were observed in 6 children (18%); in 2 cases (4%) there was a decreased mandibular angle. No intraosseus neurofibromas were detected.

These findings could represent the manifestation of a mesodermal dysplasia, in the sense of “altered growth” (without direct association with the neurofibromatosis tissue) in agreement with the features of the jaw previously reported in patients with NF.

No alterations in the bone structure were found in the control group.

**Conclusion**

According to our data, NF1-related oral manifestations are present during childhood, even if some of the best known, like neurofibromas, are not yet developed. Paediatric dentists should be aware of the characteristics of the disease in children, in particular about the poor oral hygiene conditions, the malocclusions and the radiological findings in order to prevent complications and to manage...
the therapies in a better way. Moreover they should monitor the patients with a long-term follow-up to screen the possible development of other lesions in the hard and soft tissue.

References


