

Long-term Stable Unilateral Mandibular Deformity Associated With Ipsilateral Skull-base Soft-tissue Lesion and Degenerated Pterygoid Muscles in Neurofibromatosis Type 1

REINHARD E. FRIEDRICH^{1*}, FELIX K. KOHLRUSCH^{1*}, CHRISTIAN HAGEL² and MANFRED GIESE³

¹Department of Oral and Craniomaxillofacial Surgery, Eppendorf University Hospital, University of Hamburg, Hamburg, Germany;

²Institute of Neuropathology, Eppendorf University Hospital, University of Hamburg, Hamburg, Germany;

³Department of Oral and Maxillofacial Surgery, Army Hospital Hamburg, Hamburg, Germany

Abstract

Background/Aim: Neurofibromatosis type 1 (NF1) is a tumor predisposition syndrome characterized by neoplasms originating from nerve sheath cells. The autosomal dominant hereditary disease also affects numerous developmental and metabolic processes, for example in the bones. The aim of the study was to document the diagnosis and treatment of an NF1 patient who had developed a space-occupying lesion at the base of the skull with noticeable mandibular changes.

Case Report: The patient, who presented for her initial examination as a teenager, had an asymmetrical lower face. The deformation of the lower jaw mainly affected the left ramus and was associated with a deviation of the chin region toward the affected side. MRI revealed a diffuse plexiform neurofibroma (PNF) on the left side, which spread within the dystrophic pterygoid muscles. Over a treatment interval of 21 years, the patient developed numerous PNF in various regions of the body. The extent of the skull base tumor and the degree of muscular dystrophy remained constant during this period. Similarly, the mandibular dysplasia already noted during the initial examination remained unchanged.

continued

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*These Authors contributed equally to this work.



Prof. R.E. Friedrich (ORCID: 0000-0001-7747-9636), MD, DMD, PhD, FEBOMFS, Department of Oral and Craniomaxillofacial Surgery, Eppendorf University Hospital, University of Hamburg, Martinist. 52, 20246 Hamburg, Germany. Tel: +49 40741053259, e-mail: rfriedrich@uke.de

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Conclusion: Although mandibular dysplasias associated with PNF are rare findings in patients with NF1, they often have a characteristic pattern and may remain unchanged for decades. Knowledge of tumor-associated mandibular dysplasia in patients with NF1 is essential for the differential diagnosis of tumors in this region which can become malignant.

Keywords: Neurofibromatosis type 1, mandible, magnetic resonance imaging, panoramic radiography, plexiform neurofibroma, masticatory muscles.

Introduction

Neurofibromatosis type 1 (NF1), an autosomal dominant hereditary tumor predisposition syndrome, is diagnosed in approximately 1:3,000 individuals. The penetrance of the disease is complete, while the phenotype varies considerably. The gene locus is on chromosome 17q11.2. The gene product is called neurofibromin (1). Among its known functions, the protein primarily inhibits the rat sarcoma (RAS) protein. Restriction or loss of RAS inhibition increases cell proliferation and is a frequently observed step in the pathogenesis of neoplasia and complex dysplasia in humans. NF1 is characterized by the frequent occurrence of neurogenic tumors called neurofibromas. It is assumed that these tumors arise from Schwann cells or their precursors. According to previous research results, these tumors develop after the allelic loss of the *NF1* gene and further mutations that impair the function of genes with tumor suppression effects (2, 3).

Beyond its classification as a tumor predisposition syndrome, NF1 is also a syndrome in which development and function of organs can be affected, for example, bone homeostasis (4-6). It can be difficult to differentiate between tumorous bone changes and osseous developmental disorders, for example in the case of scoliosis of the spine, which occurs frequently in NF1 (7).

This patient report is intended to complement the spectrum and pattern of NF1-associated craniofacial bone deformities. Reference is made to the highly variable phenotype of musculoskeletal changes in the facial skull, which are caused by a tumor that is pathognomonic for NF1, namely diffuse plexiform neurofibroma. The mandibular deformity described here is presented as the

result of neuro-osseous interactions (8), in which tumor-induced dystrophy of the masticatory muscles during bone development likely contributes significantly to the characteristic phenotype.

Case Report

Clinical report. The female patient, who was 16 years old at the initial examination, presented with discreetly visible facial asymmetry, mainly affecting the chin area. The chin was slightly shifted to the left side. In contrast, the tip of the nose was slightly shifted to the right. At the time of admission, the child of a father suffering from NF1 showed café-au-lait spots. The adolescent had no functional impairment in the maxillofacial region. The tongue surface was unremarkable on inspection. The panoramic radiograph (PR) revealed a deformation of the mandibular ramus and condylar process region on the left side. Here, the condyle and condylar head were significantly dysplastic. In addition, the antegonial notch on the left side was deepened (PR and lateral cephalogram). The most striking finding was an approximately triangular translucency of the left ramus, with its tip pointing caudally. It had a broad base in the intercondylar region and tapered toward the mandibular foramen. On the PR, the left mandibular canal ended without any visible change in diameter at the caudal tip of the triangular translucency of the ramus. During the initial examination, previous cranial magnetic resonance imaging scans (MRIs) were evaluated for the 13-year-old girl. These images showed that the pterygoid muscles on the tumor side were hypoplastic. A structureless, hyperintense area located between the residual muscles and the thinned



Figure 1. Clinical documentation of facial findings. (A) En face view of the 16-year-old patient with noticeable deviation of the chin region to the left side. Symmetrical shape of the orbit and soft tissue of the region. The pinnae are symmetrically developed and fixed parallel to the horizontal plane. (B) En face view of the 34-year-old female patient with stable lower face asymmetry. (C) Oral aspect with mouth open shows the symmetrical position of the lower jaw teeth. The deviation of the teeth of the lower jaw – measured as the deviation of the contact surface between the central incisors from the median sagittal plane – towards the affected side is minor. (D) Symmetrically shaped dental arch of the upper jaw (one premolar is missing on each side).

bone was striking. In continuity with the hyperintense lesion, isointense strip-like lesions were visible between residual muscle strands of the pterygoid muscles. The isolated, frayed muscle strands were separated from each other by hyperintense space-occupying lesions which were arranged approximately parallel to the muscle strands and whose signal intensity corresponded to that of fatty tissue. The hyperintense area primarily affected the lateral pterygoid muscle and the upper portion of the medial pterygoid muscle. The findings were assessed as fatty degeneration of the masticatory muscles in diffuse neurofibroma (MRI). Based on information from the literature (9) and our own experience in treating patients with NF1 (10), the skeletal findings (PR) were considered a complex radiological sign associated with clinically inconspicuous neurofibroma (MRI). The patient had no symptoms and was referred to further regular monitoring. Ten years later, the patient returned for diagnostics, where the clinical and radiological findings were confirmed as unchanged. Since her first consultation the patient had developed several small symptomatic nodular plexiform neurofibroma, which were removed (occipital/nuchal region). At the ages of 26 and 34 years, the patient returned for further surgical consultation regarding the syndromic disease. Clinical examination of the facial and oral regions, as well as planar radiographic imaging, confirmed the stability of the dental findings and

mandibular deformity on the left side over a total interval of 21 years. Detailed radiological analyses of the mandible revealed anatomical variations of the nerve canal (vide infra). The dorsal maxilla (tuber region) on the affected side was physiologically shaped and symmetrical to the opposite side throughout the entire examination period. When comparing the MRI scans taken over the whole period, MRI showed largely identical diffusely infiltrating lesion of the pterygoid muscles, particularly in the upper portion of the muscle masses, on the affected side. The lesion did not change in volume or texture over time. MRI scan ruled out a lesion of the brain stem or Gasserian ganglion. Numerous neurofibromas of the adult woman were removed during the last consultations, including a left retro-auricular plexiform neurofibroma (PNF). At no point did the patient experience sensory disturbances in the facial area. The adult patient complained of chronic pain in her lower extremities. Repeated electromyographic examinations revealed a proximal conduction disorder in the legs and, in the 34-year-old patient, motor conduction damage to the right peroneus muscle.

Figure 1 shows the clinical findings; Figure 2 shows skull findings from plain radiography; Figure 3 shows MRI findings of the skull over 21 years; Figure 4 shows the skeletal dysmorphia of the examined region in the three-dimensional skull reconstruction; Figure 5 shows the mandibular opening of the nerve in the ramus and the

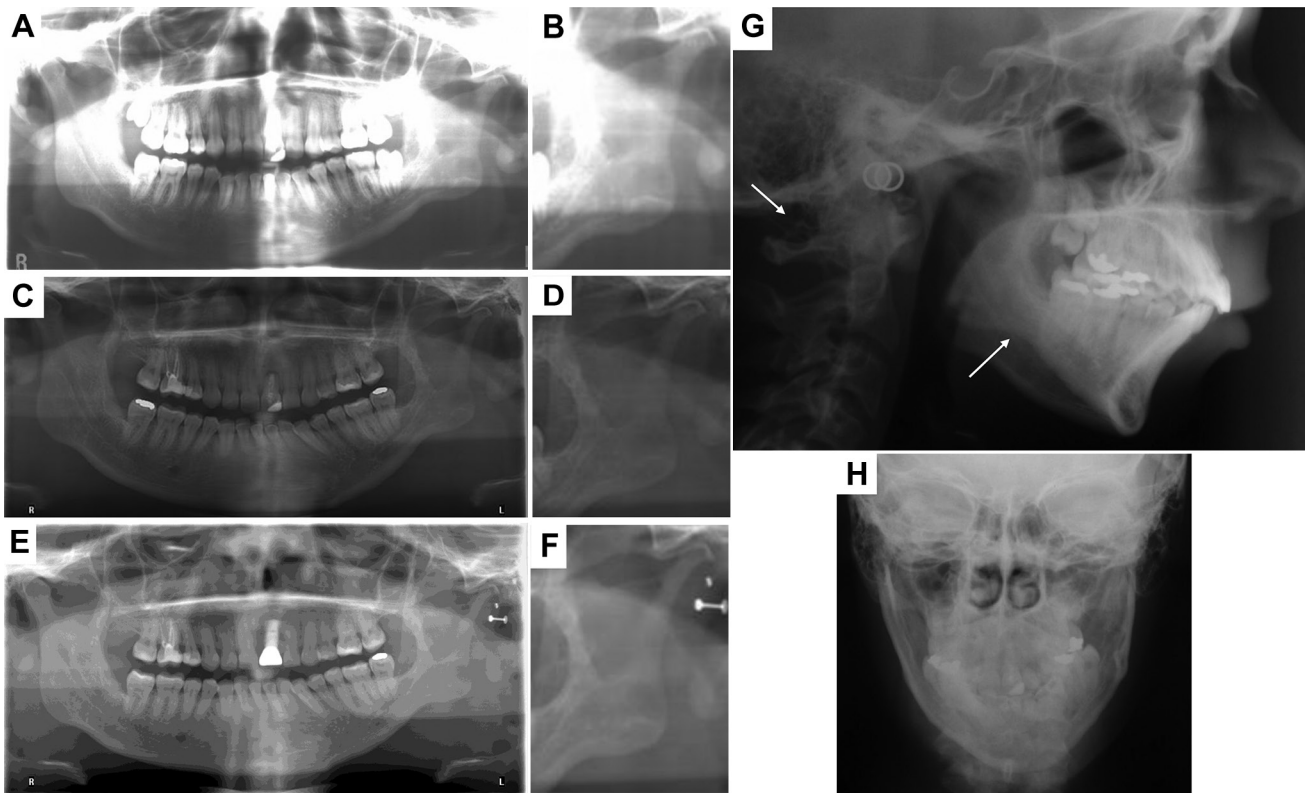


Figure 2. Representation of the jaw and skull on plain radiographs [(A-F): Panoramic radiographs (PR), (G-H): Cephalograms. Figures B, D, and F are detailed images of the distal parts of the left mandible, as shown in the overview image identified in alphabetical order above]. Figures A-F show a deformed region of the left ramus and mandibular angle. Noteworthy features include: narrow capitulum, elongated collum inclined basally toward the anterior, broad coronoid notch, triangular brightening of the bone from the coronoid notch to the proximal end of the nerve canal in the vertical plane, shortened dorsal ramus margin, and vertically deepened antegonial notch. The proximal end of the nerve canal is significantly lower on the affected side than on the right side (51). The right mental foramen is larger and lies further caudally than the left one. The left mandibular region, enlarged in the sectional images (B, D, F) of the PRs, remains unchanged over the course of 18 years. (G) The lateral cephalogram shows increased basal retraction of the mandible on the affected side (lower arrow). The patient's pons is complete (upper arrow). (H) The posterior-anterior cephalogram shows asymmetry of the lower jaw, with the left jaw further away from the median sagittal line than the right jaw. The orbital region is symmetrical.

distribution of the nerve branches after entering the bone; Figure 6 shows the histological findings of a cutaneous tumor that had developed dorsally adjacent to the temporomandibular joint in the adult patient. The results of the individual investigations are as follows:

Facial symmetry. The patient was photographed several times using standardized recording techniques. In the *en-face* image of the 16-year-old adolescent (Figure 1A), with the head tilted slightly to the left, the displacement of the chin region to the left is noticeable. The radiological

examination [computed tomography (CT), cone beam computed tomography (CBCT)] ruled out asymmetry of the orbits. Therefore, the bi-pupillary line was used as the horizontal cephalometric reference line. The median vertical line was defined as the line running perpendicular to the bi-pupillary line through the center of the anterior frontal bone prominence. This point was constructed as the midpoint of the line connecting the outermost points of the visible medial eyebrow borders. The coordinates showed that the quotient of the intercanthal distances to the median sagittal line was 1, and the quotient of the temporal

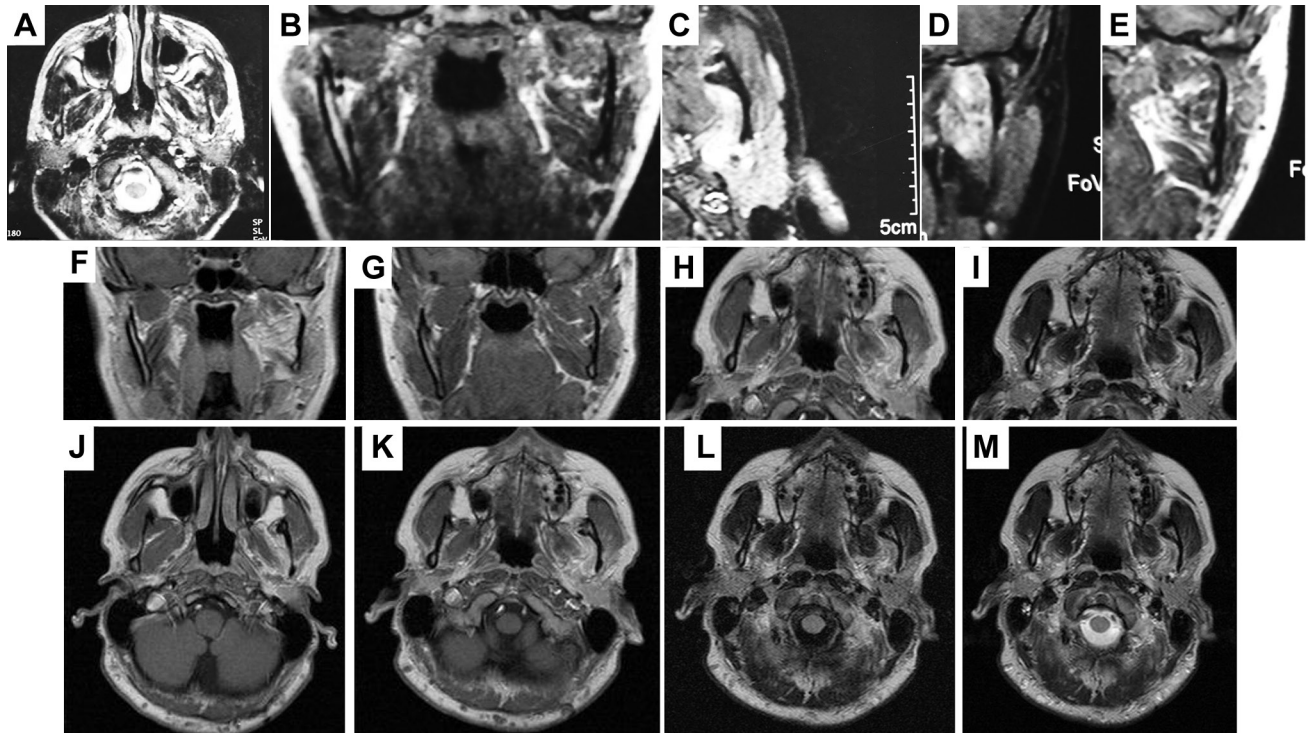


Figure 3. MRI images of the skull base region taken over a period of 21 years. (A-B): The thirteen-year-old patient shows dysplasia of the pterygoid muscles on the left side (axial slice). (B) The coronal slice clearly shows that the pterygoid muscles on the left side are primarily affected in the cranial part. The ramus shown in the image appears narrower than that on the opposite side. (C-E) In the 16-year-old female patient, the space-occupying lesion is more clearly visible. (C) Complementary to the arcuate deformation of the left ramus, a hyperintense space-occupying lesion is shown, the volume of which has developed at the expense of the medial pterygoid muscle. (D) shows an inhomogeneous, hyperintense space-occupying lesion 1.9 cm wide and 4 cm in craniocaudal extension. (E) Another section shows the diffuse infiltration of the space-occupying lesion into the adjacent musculature. (F-I) Representative images of the skull base show the stable pathological findings of the 25-year-old patient in various registrations in the coronal (F, G) and axial (H, I) planes. The space-occupying lesion also remains stable in the 34-year-old patient (J-M). The left masseter muscle is not affected by the space-occupying lesion. [F-G, J: spin-echo sequence (T1), I and M: turbo-spin-echo sequence (T2), L: tirm (Flair) sequence (turbo spin echo recovery magnitude/fluid attenuated inversion recovery (T2))].

distances to the center (defined as the intersection of the extension of the bi-pupillary line to the lateral contour border of the periorbital skin) was 1.02 in favor of the right side. The same value in favor of the same side resulted from the ratio of the distances between the philtrum and the lateral cheek border (1.02). While the symmetrical comparisons for orbit and midface described variations that can be considered physiological, the deviation of the chin to the left side was clear. The ratio of the midline to the lateral border of the chin skin was 1.61 in favor of the left side [reference point: 1 cm above the tip of the soft tissue chin (on p.a. cephalogram: 1.84)]. However, the tip of the

nose deviated to the right side. In the adult woman, the symmetry of the orbital and zygomatic regions and philtrum was confirmed according to the reference points and distances. The soft tissue chin deviation quotient had decreased slightly (ratio: 1.23), although the direction of deviation had remained the same (Figure 1B). The oral images show symmetrically formed dental arches, an inconspicuous tuber region on the left side, and missing premolars on both sides (Figure 1C and D).

Anatomical areas on radiological images. Imaging of the region of interest was based on MRIs (age: 13, 16, 25 and 29

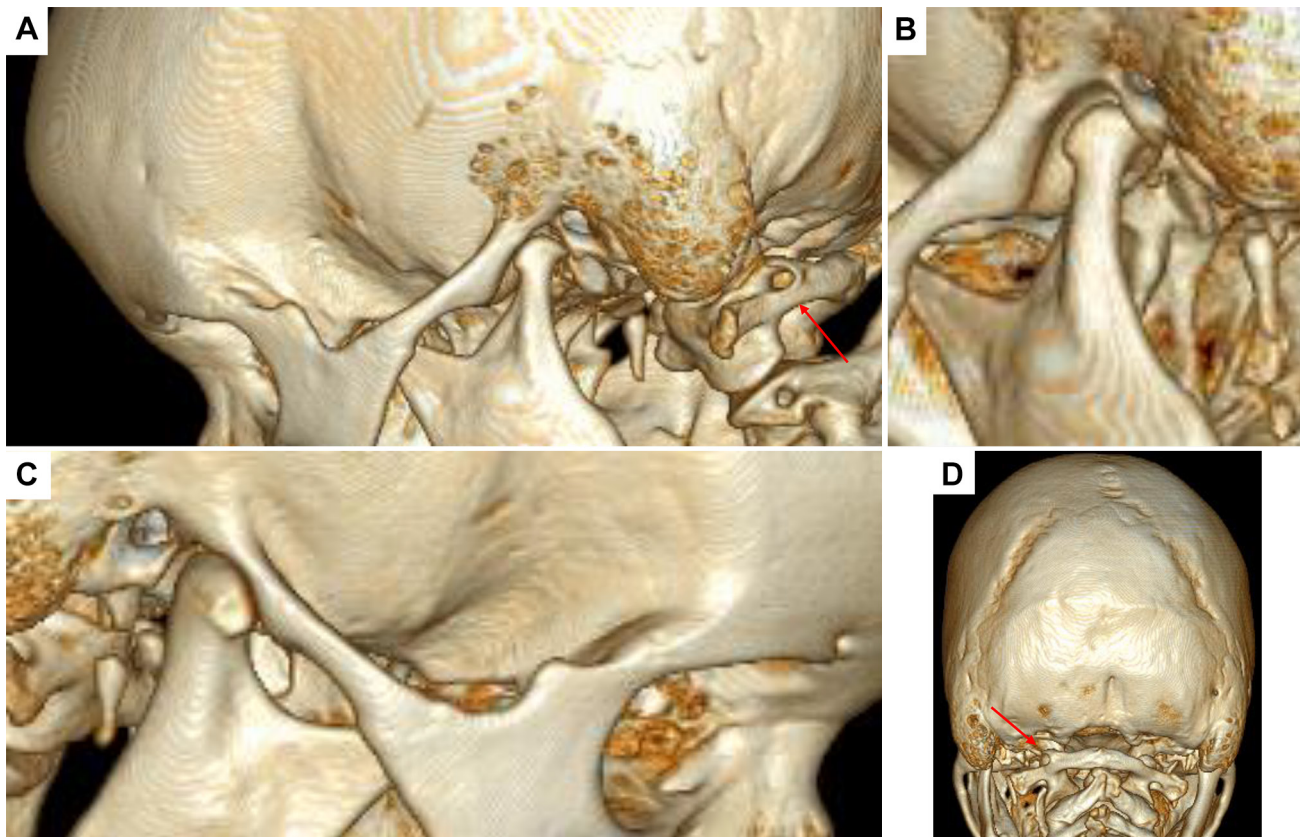


Figure 4. Three-dimensional skull surface reconstructions. (A) In the lateral view of the left temporomandibular joint region, the slender, elongated collum and the delicate capitulum are noticeable. The distal region of the glenoid fossa is pneumatized, and the tuber articulare is normally developed. The arrow shows the poniculus posticus on the left side. (B) Detail of the temporomandibular joint region with a slight shift of the perspective toward the dorsal side. This perspective shows the disproportion between the articular process and the normally shaped articular fossa. (C) The right angle of the jaw shows an unremarkable condyle and illustrates the comparison with the tumor-side deformed coronoid notch (A). Furthermore, the side-by-side comparison shows the symmetrical development of the zygomatic arch and bony auditory canal. (D) The occipital view shows symmetrically ossified lambdoid suture and the equally symmetrical contour of the zygomatic arches. The image confirms the unilateral development of the poniculus posticus (arrow).

years), PA (age: 16, 29, and 34 years), cephalogram (age: 16 years), CT (age: 26 years), and CBCT (age: 29 and 34 years).

Orbit. The CT and CBCT images showed symmetrical orbits with physiological fissures and foramina of normal width (Figure 1H). The MRI showed physiological soft tissues of the eye sockets and the periorbital region of normal structure and size. The optic nerves were unremarkable in diameter and signal.

Zygomatic arch and glenoid fossa. During the whole examination period, neither the zygomatic arch nor the

articular cavity of the temporomandibular joint (TMJ) was altered on the tumor side (Figure 4A and B). Obviously, the skull base lesion had not reached the zygomatic arch as visible on the MRI (Figure 2, Figure 3, and Figure 4). The skeletal symmetry of the lateral midface was clearly assessable in the CT-generated three-dimensional representation of the skull surface (Figure 4). The masseter muscle on the affected side was normally feathered and had the same volume as the muscle on the opposite side (MRI) (Figure 3).

Capitulum, condylar neck, and coronoid notch. In the child, the capitulum of the tumor side was pencil-shaped and

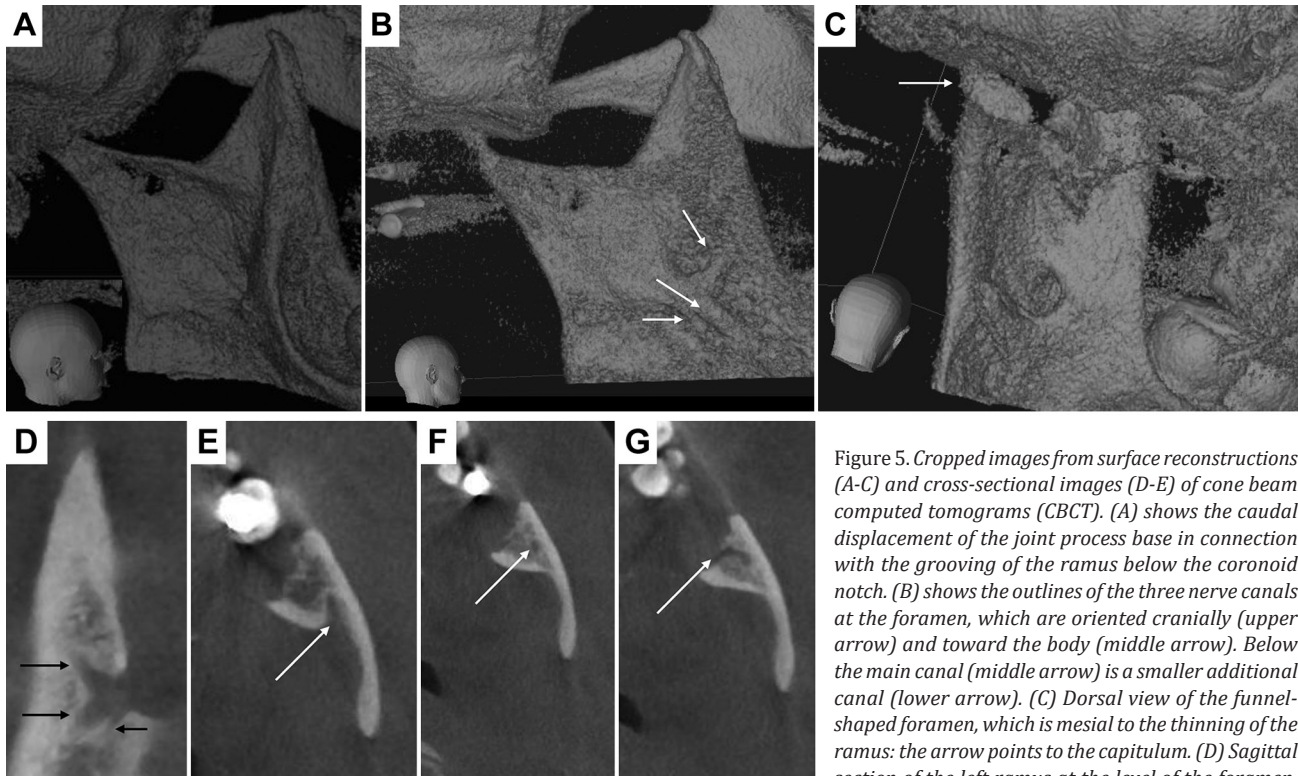


Figure 5. Cropped images from surface reconstructions (A-C) and cross-sectional images (D-E) of cone beam computed tomograms (CBCT). (A) shows the caudal displacement of the joint process base in connection with the grooving of the ramus below the coronoid notch. (B) shows the outlines of the three nerve canals at the foramen, which are oriented cranially (upper arrow) and toward the body (middle arrow). Below the main canal (middle arrow) is a smaller additional canal (lower arrow). (C) Dorsal view of the funnel-shaped foramen, which is mesial to the thinning of the ramus: the arrow points to the capitulum. (D) Sagittal section of the left ramus at the level of the foramen.

The upper arrow points to the canal that runs into the muscular process. The middle arrow shows the main branch; the lower arrow shows the additional canal. Figures E-F show the course of the upper canal: (E) shows the lingual opening at the foramen, (F) the course in the base of the process, and (G) the opening at the front of the ramus (29-year-old patient).

incongruent with the joint surface (PR, Figure 2A-F). The distance between the articular process and the articular surface was greater on the deformed side. The joint space between fossa and capitulum surface was widened on the cranial and distal aspect of the affected side [distances: anterior: right: 2.66 mm, left: 2.60 mm; cranial: right: 2.77 mm, left: 3.1 mm; dorsal: right: 3.75 mm, left: 5.55 mm (reference points of measurements: The vertical distance was the distance from the highest point of the capitulum to the fossa in the vertical sagittal X-ray section (cranial); anterior/posterior measurements were taken at 45° to the extended vertical reference line of the cranial measurement point; average values from three individual measurements, 34 years, CBCT)]. The three-dimensional bone surface reconstruction of the left TMJ illustrated the position of the capitulum and fossa (Figure 4A-B). The

transition from the capitulum to the joint neck was only slightly pronounced. The condylar neck was tilted anteriorly, giving the impression that this bone section through its deformation had compensated for the sagittal shortening of the affected corpus side. The coronoid notch, which was elongated in the anteroposterior direction, had a slightly lower vertical position than the opposite side (PR). The temporal muscle on the affected side was normally feathered and had the same volume as the muscle on the opposite side (MRI).

Ramus. On the PR, the left-sided ramus translucency approximated the shape of an isosceles triangle with the tip pointing caudally (Figure 2A-F). The base provided the connection between the processes. The translucent coronoid notch (semilunar incisura) remained constant

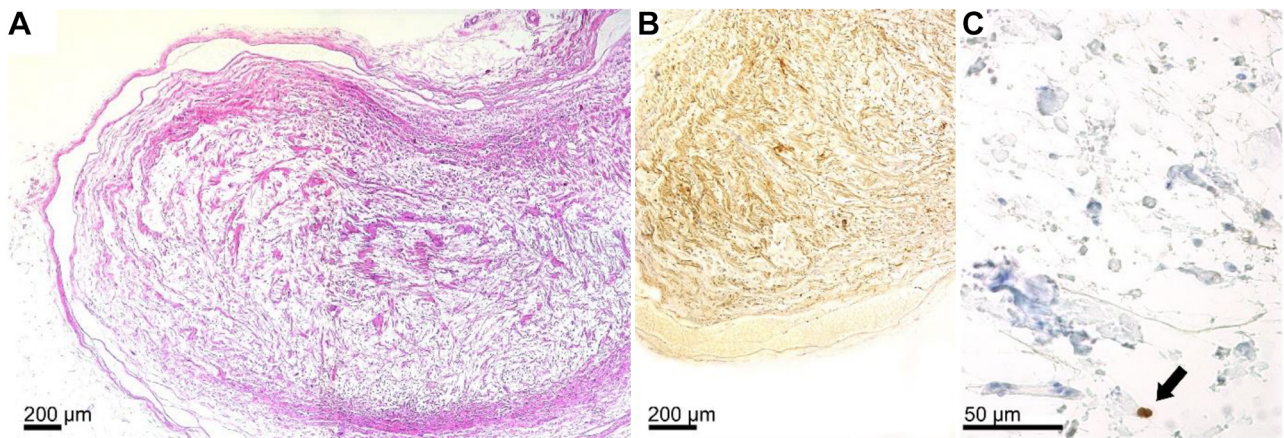


Figure 6. Histology of left retroauricular lesion. Histological presentation of the surgical specimen. (A) Nerve fascicle infiltrated by a tumor composed of long spindle shaped cells grown in a loose myxoid matrix, note the thickened perineurium (hematoxylin and eosin stain). (B) Immunohistochemical labelling (brown staining) of the tumor cells with S100-antibodies (chromogen diaminobenzidine). (C) Nucleus labelled with the proliferation marker Ki-67 (arrow, chromogen diaminobenzidine).

in shape in the examination interval on this radiological projection. The radio-translucency of the left ramus was homogeneous. The radiodensity and location of the structure appeared like a widely caudally extending medial sigmoid depression, as described for this radiological projection (11, 12): see the sigmoid depression on the right side for comparison. The overall length of the left posterior ramus was shortened (right side: 5.56 cm, left side: 4.38 cm, 34 years old patient, PR). The sectional images clearly showed the lingual depression of the ramus as the cause of translucency on PR. On CBCT, the thinning of the ramus mainly affected the lingual side, showing a local increase in the transverse diameter of the bone around the foramen (Figure 5). In the lateral view of the skull, the tip of the left coronoid process extended further cranial than on the right side (Figure 4 and Figure 5). The three-dimensional reconstruction of the bone surface based on CT data showed an intact lateral bone surface with no noticeable changes to the contour (Figure 4).

Mandibular foramen. On the PRs of the adult patient, the right mandibular canal opened as a cup-shaped foramen at the transition from the middle to the upper third of the ramus. The narrow main canal on the left side ended at

the base of the (lingual) depression of the ramus, approximately at the level of the crown surface of the second molar (PR) (Figure 2). The termination of the tubular canal (defined as the lingual opening of the canal in the ramus) measured using CBCT was smaller on the left side than on the right side (Table I). The channel's opening was the bottom of a bowl-shaped bone depression located in the dorsal extension of the nerve canal. This bone funnel resembled a deformed mandibular foramen (Figure 5C and D). However, MRI scans of this region throughout the course of the examination showed a hyperintense space-occupying lesion between the dysplastic medial pterygoid muscle and the bone, which nestled against the deformed ramus, including the foramen region, without this signal being visible within the bone (Figure 3). In other words: the hyperintense signal of the lesion was not present in either the foramen or the nerve canal. This finding raises doubts as to whether this presumed neurogenic space-occupying lesion extended to further distal parts of the nerve. To supplement the assessment of the lesion at the entrance to the inferior alveolar nerve, it is useful to characterize the boundary of the nerve canal at the transition to the lingual bone surface (Figure 2, Figure 5). The lingual cortical bone was of the same thickness as that on the

Table I. Measurements of the foramina and the mandibular nerve canal on cone beam computed tomograms (CBCT) of the 29-year-old patient.

	Mandibular foramen		Mental foramen		Mandibular canal	
	Right	Left	Right	Left	Right	Left*
Maximum diameter on coronal section	0.62 ¹	0.75 ¹	0.30	0.18	0.30 ²	0.26 ²
Maximum diameter on axial section	0.45	0.25	0.40	0.25	0.36 ³	0.22 ³
Maximum diameter on sagittal section	0.82	0.32	0.69	0.28	0.47 ⁴	0.32 ⁴

Values in cm. All measurements of canal are rectangular distances between the cortical boundaries of the canal connecting cortical points of the canal's wall. ¹Reference points: lingula tip. ²Reference point: Mid ramus, measurement on same horizontal level for both sides. ³Reference point: Adjacent to dorsal root of inferior second molar. ⁴Reference point: Below distal root of inferior second molar. *Main canal.

right side. This cortical bone transitioned homogeneously into the thinner cortical border of the lingual side of the canal. The most proximal part of the main channel's lateral cortical boundary ended in an area where the outer border of the ramus bone had developed a broad layer of cancellous bone. Axial section imaging showed that the shell-like thinning of the bone only began after the canal had opened into the para-mandibular space (not shown). In this case of characteristic NF1-associated ramus deformation, a distinction must be made between the lingual depression of the ramus and the opening (foramen) of the canal (Figure 5C). Only after the canals opened onto the lingual bone surface did the shell-like thinning of the lingual bone aspect develops. The foramen (defined as the summed up lingual openings of the canals in the ramus, Figure 5D) on CBCT was significantly larger on the left side than on the right side. However, the opening of the mandible's main canal was significantly narrower than that on the opposite side (Table I).

Mandibular canal. Both the main canal of the nerve and a second canal, which was depicted caudally to it, opened into the left mandibular foramen (bifid canal). The accessory canal fused into the main canal in the premolar region. The findings can only be suspected on the PRs and were clearly demonstrated on the sagittal sections of CBCT (Figure 2 and Figure 5). On the right side, a retromolar canal branched off at a right angle from the single main canal. The left main channel had a smaller diameter than the single right channel (Table I).

Interestingly, a narrow retromolar canal branched off from the main canal at an acute angle in the left side of the jaw angle, extending to the rear root of the second molar. However, another nerve canal originated from the lingual opening of the nerve canal in the ramus. The third canal was located above the main canal and ran cranially into the muscular process. The sectional images showed a rapidly narrowing canal that extended to the front edge of the process and opened onto the surface there (Figure 5E-G). This canal, which was directed toward the muscle process, was not shown on the PRs. The ratio of the diameters of the three canals (coronoid process/main canal/accessory canal) at the orifice is approximately 2:3:1 (CBCT).

Mental foramen. On PR, the right mental foramen was a landmark identifiable throughout the entire examination period and appeared to have a constant radio-morphological structure (Figure 2A and E). It was located apically to the second premolar and had a transverse-oval translucency. The foramen on the left side was significantly smaller in diameter and was located further cranially than the right one, slightly medial to the root tip of the second premolar (Figure 2A and E). On the PR of the adult patient, the bifurcation defining the short ascending canal to the mental foramen and the anteriorly directed horizontal branch of the incisal canal was clearly visible on the left side (Figure 2E). However, the mental foramen on the left side was much less clearly visible than the right on PRs. On CBCT, the left foramen diameter was smaller than the

right (Table I) and no additional mental foramen was detected on either side.

Anatomical variant of the atlas vertebra (C1). On the lateral cephalogram of the 16-year-old patient, the complete left *ponticulus posticus* was already identified (Figure 2G, Figure 4A and D). The CT-generated surface representation of the dorsal skull and spine demonstrated the unilateral nature of the finding on the lesion side (Figure 4D).

Histology. For neuropathological examination a total of 2 ml of specimens measuring up to 8×8×10 mm³ were sent in. The specimens were white and showed glassy surface. Some specimens had a cartilage-hard consistency.

Upon histological examination several tumor infiltrated nerve fascicles with intact perineurium and adjacent fatty tissue were noted. The tumor was of low cellularity and had a myxoid matrix with focal areas of marked fibrosis. The tumor cells appeared spindle-shaped with wavy contours and small hyperchromatic curved nuclei. There was no evidence of mitotic activity and no siderin deposits were noted.

Immunohistochemical examination showed strong expression of S100 protein in the tumor cells. The perineurium of the nerve fascicles was labelled with antibodies against epithelial membrane antigen (EMA). Residual axons stained positive for neurofilament. A low proliferative activity was demonstrated with Ki-67 antibodies, which labelled approximately 1% of the tumor cells. The diagnosis was a plexiform neurofibroma with exclusively intraneural growth.

Discussion

The described disease course shows that a facial neurogenic tumor that had developed early in life of a symptomless patient with NF1 can remain stable for a long time and does not require surgical treatment. In this case, surgical exploration was not necessary because no significant changes in the findings developed over time. Detailed descriptions of both the diagnostically significant

typical combination of skeletal findings in the jaw (13, 14) and the soft tissue lesions associated with skeletal malformations (15, 16) for NF1 patients are now available, so that a diffuse plexiform neurofibroma with characteristic skeletal dysplasia was diagnosed.

This case differs from the previous report of tumor spread involving the entire masticatory muscles and progressive local osteolysis (jaw angle) in adolescence and early adulthood (17). In that case, after augmentation osteoplasty of the bone defect, there was no further osteolysis in this area, and the contour of the affected jaw angle/ramus region, like the case presented here, also remained unchanged for decades. Similarly, the presented stable musculoskeletal dysplasia differs from another case of slowly resorbed, tumor-encased ramus and distal corpus in hemifacial PNF in early adulthood in a patient with NF1 (18), as well as the rapid osteolysis of the ramus in NF1-associated malignant peripheral nerve sheath tumor (MPNST) (19). While the first two case reports described musculoskeletal changes that had been known since childhood or adolescence (17, 18), MPNST developed in an adult patient with NF1 without visible jaw deformity (19). Another difference from the previous reports on mandibular dysplasia in NF1 is the unusual course of the inferior alveolar nerve.

Association between mandibular dysplasia and plexiform neurofibroma in NF1. The tumor observable in imaging appeared associated with the peripheral distribution of the trigeminal nerve's third branch at the skull base. The discreet skeletal changes are likely local effects of tumor on a developing bone [joint area, ramus (13)] as well as indirect effects due to shortening of the mandibular body in the sagittal dimension and ramus in vertical dimension causing deviation of the chin midline towards the tumor side (20). However, MR imaging limited the definition of the extent of the lesion to the area between the base of the skull and the point of entry of the inferior alveolar nerve into the bone. Neither the oral findings nor the external appearance of the patient provided any indication of a more peripheral manifestation of a neurofibroma on the

affected side. Further evidence for this assessment is provided by the examination of the radiological skull images whereby two-dimensional overview images provide valuable information about skeletal pathology. The standardized cephalometric skull image showed not only the narrowing of the corpus on the lesion side (in the vertical dimension, antegonial region, lateral view), but also the shortening of the left half of mandibular corpus with a consequent shift of the midline of the chin toward the lesion side (posterior-anterior view). These skeletal effects are to be expected in NF1 patients with diffuse PNF of the third trigeminal branch (20). In fact, the healthy mandibular ramus is considered a bilaterally symmetrical bone (21). Deviations from symmetry are evaluated as functional adaptations of the moving bone (22) or are signs of pathologies that require clarification. The overview image of the permanent dentition (PR) shows that the correctly developed dental arch, which fully occludes with the opposing teeth, has been achieved by mesial tilting of the posterior teeth on the affected jaw side (Figure 2A, C, and E) (a distortion effect of the tooth positions caused by the examination procedure due to positioning errors or different positioning of the dysplastic and normal jaw halves in relation to the diagnostic trough of the PR is unlikely: the ratio of the tooth crown diameters of the first premolars at the enamel-cementum junction is 1.08).

Noteworthy is the tumor infiltration of the pterygoid muscles and the marking of the lesion by signal conveyance corresponding to that of adipose tissue. Directly adjacent to the deformed ramus/condylar process, this lesion is homogeneously isointense to adipose tissue on MRI, mainly located between the bone and the pterygoid muscles and situated between the separated muscle fibers. In retrospect, the lesion appears as a complex of neural, muscular, and skeletal changes that became noticeable early in childhood and had remained largely stable during the observation period. In this case, the facial skeletal phenotype of the NF1 patient was characterized more as a bony malformation (hamartoma) than as tumorous destruction (4, 23). In fact, earlier authors have already

drawn attention to the neural control of fat cell development, and it has been shown that NF1 patients' PNF typically have an increase in adipose tissue (24, 25). The morphological experience confirms the surgical practice of debulking procedures for large diffuse PNF (13, 14). During the procedure, disproportionately large amounts of fat may make up the mass of the lesion and give the visual impression that, instead of reducing diffuse PNF, fat tissue is being reduced. The suggested coincidence of tumorous nerve sheath tumor and fat tissue (26-28) could explain the heterogenous signaling of the lesion in the MRI (29). The use of fat suppression techniques to differentiate neurofibroma from adipose tissue (30) must not negate the need of differential diagnosis of fatty tissue in the neurogenic lesion on images (31).

However, tumor-unrelated local fatty atrophy of the pterygoid muscles due to motoric nerve damage cannot be ruled out exclusively through imaging (15). Neurogenic muscle destruction could also be due to either tumorous components of individual branches of the mandibular nerve causing (partial) deletion of nerve function or nerve branch destruction from other causes such as pressure of adjacent tumor, lesions in proximal parts of the nerve or in the ganglion (32). Selective atrophy of the masticatory muscles because of damage to individual or multiple nerve branches that supply the masticatory muscles with motor function has been repeatedly described, both for idiopathic cases and as isolated finding in complex disorders (33-36). However, PNF has been repeatedly demonstrated for the combination of soft and hard tissue skull base findings on MRI/CT in patients with NF1. The pattern of mandibular dysplasia was described by Lorson (9) and Sailer (37, 38). The present report shows that in NF1 cases with less obvious mandibular and TMJ findings, supplementary diagnostics and a carefully conducted family history enable the findings to be classified for a diagnosis. Apparently, topographically restricted muscular disorders and mandibular dysplasia in NF1 fit into the concept of 'unilateral disruption of mandibular development during the time of normal facial growth' (35). These neurogenic mandibular developmental

disorders are rare, quite characteristic, and are noticeable in NF1 patients with facial PNF (13). Neurofibromas are considered rare findings in the differential diagnosis of trigeminal (motor) neuropathies (39).

The location of the lesion is like that in the report by Hisatomi *et al.* (15), who identified a lesion in the medial masticatory muscles and adjacent regions during examination of their patient with NF1. In that case, repeated surgical exploration was performed and neurofibroma was ultimately detected in the lesion. However, the authors point out that a subsequent biopsy of the suspicious region did not reveal any evidence of tumor. These results give rise to the hypotheses that in diffuse neurofibromas with a voluminous extracellular matrix, the proportion of tumor cells per volume may be low and a biopsy may fail to detect the tumor. What is comparable in both cases is the mild phenotype of the disease in the affected facial region. This finding can evidently be interpreted as an indication of the close topographical relationship between tumor development and spread and development and growth of affected organs. It is therefore likely that in the case of proximal development of the cranial peripheral nerve tumor, more distal portions of the nerve may not be affected. The case presented here provides an example of this assumption. The comparison of the referred report with detailed descriptions of the literature shows that diffuse PNF can arise far distally in the terminal area of the trigeminal nerve's branch and stay restricted to the area where they were noted first (40). These cases with distant third branch involvement lack the characteristic mandibular shape alterations noted in proximal nerve involvement (skull base) and topographically closely associated (proximal) dysplasia of the mandible by a neurofibroma in patients with NF1 (41). However, based on surgical experience, the periphery of diffuse neurofibromas can disperse as flat, wafer-thin subcutaneous lesions and extend significantly further than advanced imaging would suggest.

Zygomatic arch. The zygomatic arch typically shows changes when the temporal fossa is infiltrated by a PNF

and when the masseteric muscle originating from the arch is tumorous (13, 14). In the present case, the zygomatic arch on the tumor side is anatomically normal and symmetrical to the opposite side. From the zygomatic arch shape, it can be assumed that the masseteric muscle is not affected in the young patient and that the tumorous infiltration has not developed an extension reaching the level of the zygomatic arch.

Articular fossa. In contrast to the hypoplastic articular process, the size and shape of the fossa and tubercle are anatomically normal. The tomographic images demonstrate that the tubercle is pneumatized to its medial aspect. The zygomatic process of the temporal bone is not pneumatized. The disproportion between the size of the capitulum and the fossa is characteristic of mandibular PNF in patients with NF1 (10, 13).

Ponticulus posticus. A complete postic ponticulus is present on the affected side. This incidental finding is classified as a harmless variation of skeletal differentiation, reported in the radiological literature in about 25% of cranial radiographs (arch completed: 10.4%) and is considered a nonspecific finding (42). However, the arch-like ossification ensheathing the vertebral artery at this site has been shown to be frequently diagnosed with another tumor predisposition syndrome (43, 44). It should be examined whether the frequency of Kimmerle's anomaly in NF1 can be differentiated from the expected frequency in the normal population. Some authors point out that the finding occasionally is associated with headaches and vascular problems (45, 46).

Mandibular foramen. Several researchers have pointed out that the mandibular foramen in NF1 can be enlarged (13, 47, 48). The finding was evaluated both in case series and studies with a larger number of NF1 patients assessed for mandibular changes (13, 16, 38, 47, 49-52). In the case presented, the lateral bone surface of the ramus was intact. Other authors report tumor-associated perforation of the lateral cortical boundary of the ramus, giving the

impression of a foramen directed toward the lateral surface of the bone (53). The apparently individually variable tumor-associated bone deformation/defect gives rise to the need for extended diagnostics when identifying these skeletal findings (asymmetrical foramina, ramus translucency, bowing) on overview images of the jaw, especially considering the development of a malignant tumor from a PNF that originated in this region (19).

Mandibular canal (Visibility, shape, and size). An enlarged nerve canal on PR in patients with NF1 does not depend on evidence for ipsilateral inferior alveolar nerve PNF (10, 13, 47). However, to date the descriptions of NF1-associated enlarged nerve canals do not consider whether the patients' calcium metabolism was altered, compensated by medication, or whether the cases involved osteoporosis. The calcium content of the bone can influence the visibility and limitation of the nerve canal on radiographs (54, 55). In this respect, it is still unclear how the pathogenesis of an enlarged nerve canal in NF1 can be explained.

A bifid mandibular canal has already been documented in a patient with NF1 (10, 50). According to the analysis of numerous studies on the subject in the general population, the prevalence of bifid canals in the mandible appears to be highly variable, depending on ethnicity, and the examination technique used. The estimated total prevalence of bifid canals is approximately 18%. The detection rate of bifid canals is higher on CBCT than on PR (56). D'Ambrosio *et al.* described a branching of the nerve canal based on PRs in nine patients (24%) with neurofibromatosis. Those authors interpreted the high prevalence of this finding in their study as an indication of neuroectodermal differentiation disorders in neurofibromatosis (50).

Mental foramen. The enlarged mental foramen is considered a diagnostic indicator for skeletal findings of NF1 in the jaw area (48). This conclusion is supported by clinical studies (47, 52). However, the presented report shows that the known biological variability of the

mandibular canal and its foramina must be considered in patients with NF1. A literature review of 174 cases of neurofibromatosis reported that in two cases the mental foramen could not be identified and in another two cases it was very unclear (10). To the authors' knowledge, the extent to which small mental foramina may also belong to the spectrum of mandibular findings in NF1 has not yet been investigated.

Dentition. PNF of the trigeminal nerve with spread into the oral cavity can constitute an obstacle to tooth movement. This phenomenon frequently affects impacted teeth (10, 13). The undisturbed dentition of the permanent molars and their alignment in an arch with approximal contact of teeth on the lesion side is an indication that the tumor probably does not extend to the oral cavity (57, 58). However, after complete tooth emergence, gingival neurofibromas may develop, which can lead to local changes in tooth position (40).

Malignant peripheral nerve sheath tumor (MPNST). MPNST of the trigeminal nerve is rare. The vast majority of trigeminal MPNSTs occur as sporadic neoplasms, although reviews show that individual cases with NF1 must be considered (59). Trigeminal MPNSTs have been reported in patients with NF1 as early as childhood (60). Osteolysis of the mandibular ramus in cases of sporadic MPNST of the third trigeminal branch may show similarities to the radio-translucency of this mandibular segment in cases of convex curvature caused by deformation and thinning of the bone because of associated PNF in NF1 (19). Therefore, any skeletal deformities of the mandible evident on plain radiographs in patients with NF1 should be further defined by additional imaging. Currently, MRI best meets this requirement (61, 62).

Imaging of head and neck lesions in NF1. Current recommendations for screening pediatric patients with NF1 favor MRI, with whole-body scans playing a significant role in determining tumor burden (61, 62). However, tumors and associated lesions may be small and more

difficult to detect when detectors cover a large body area. MRI based research of NF1 associated lesions in the head and neck region currently focuses primarily on the identification of intracerebral lesions and dysmorphia as well as the assessment of the optic nerve (63). In NF1, the actual screening imaging of the head and neck region should also adequately cover and assess disease-associated lesions of the skull base and the more caudal aspects of this region, *i.e.*, the face and neck (64).

Diagnostic and therapeutic significance of identifying mandibular dysplasia in NF1. In the head and neck area, extensive neurofibromas often result in considerable dysfunction and severe impairment of facial aesthetics. This type of neurofibroma, described as “diffuse” and “plexiform”, are most likely congenital lesions (3, 4, 16, 65). If the craniofacial area is affected in NF1, slight facial asymmetries or even tumors are often already noticeable at birth (66). PNF are progressively infiltrating and destructive tumors. However, the spectrum of tumor-associated facial changes is highly variable. The assignment of the aesthetic and functional disorders to the terminal territories of the trigeminal nerve provides a valuable clinical orientation and planning aid for surgical measures (67). Craniofacial PNF is often associated with skeletal changes that correlate topographically with the extent of the neurogenic tumor (13). However, the spread of the tumor is characterized by the fact that it crosses anatomical boundaries, but not normally the midline of the face (13, 67). Indeed, there is no quantitative relationship between tumor mass and associated craniofacial bone dysplasia (10, 68). Nevertheless, there are correlations between bone changes in the respective facial skull region, and the topography of a facial, congenital/early childhood diffuse or diffuse plexiform neurofibroma (13, 67, 69, 70).

Tumor-associated changes in the jaw are complex. A detailed description of the lesions provides a basis for diagnosis. Discrete distinctions, such as those between a true enlargement of the mandibular foramen and the radiological effect of an only apparently enlarged foramen, can provide valuable information about when, how and to what extent a

congenital tumor (65) interferes with bone development, which changes are primary tumorous or secondary dysplasia (71), and on what diagnostic basis the therapeutic decisions are made (47). The distinction between enlarged foramen and pseudo-foramen can also be applied to previously published cases. In their report on intraosseous neurogenic tumors of the mandible, Che *et al.* (72) showed the cyst-like distension of the mandible caused by neurofibroma. The PR showed a translucency of the ramus, which was separated from the cyst-like bone distension by a narrow bridge of regularly structured cancellous bone (PR). The axial CT showed the shell-like thinning of the ramus, but no enlarged nerve canal (the nerve canal of the PR is of normal diameter). The retention of the molars in the cyst-like intraosseous tumor that caused bone expansion in this case report (72) confirmed the often-observed close correlation between tumor-related tooth retention and the extent of tumor spread seen early in life in NF1 patients with facial PNF (10, 13, 14, 57). The authors reported the excision of the coarse oral nerve sheath tumor, which had no relation to the ramus cavity. Significantly, the patient did not exhibit any sensory deficits in the third trigeminal nerve (72).

Another example of the different spatiotemporal effects of para-mandibular neurogenic tumors on bone development is shown in the case of another study in which bone deformation of ramus was diagnosed in patient’s childhood, but corpus dysplasia was evident only in adulthood. Those authors already assessed the mandibular canal on the affected side as enlarged in the image of the 10-year-old child (PR) (47).

The dependence of craniofacial bone changes on adjacent PNF was considered in the revised classification of diagnostic criteria for NF1, insofar as the sphenoid dysplasia previously considered a single criterion for NF1 diagnosis now only fulfills this characteristic if no PNF could be diagnosed (73). However, the term sphenoid bone dysplasia covers only partly the spectrum of clinically relevant osseous changes in the orbital/periorbital and adjacent craniofacial bone regions (13, 14, 16, 20, 72, 74). Changes in the jaws or other craniofacial bones adjacent to the sphenoid are not included in the revised classification.

While current NF1 diagnosis of orbital malformation in NF1 addresses the tumor association as the dominant factor and thus identifies the soft tissue lesion as the cause of the bone change (72), repeated observations have been reported for mandibular alterations that appear to occur both with and without (plexiform) neurofibroma (47). This assessment applies above all to changes in the foramina and canal of the mandible. Enlargement of the mandibular foramina has been highlighted as a major skeletal finding in NF1, and it has been suggested that a neurofibroma is present at this site and infiltrates the canal (13, 47, 48). However, to the authors' knowledge, this assumption on facial PNF invasiveness has not yet been confirmed by surgical exploration of the inferior alveolar nerve at the mandibular foramen or histological confirmation of tumor inside the nerve canal. However, an earlier report (10) has already pointed out that the enlarged mandibular foramen as a skeletal radiographic sign that indicates a neurogenic tumor arising at the skull base and continues in further peripheral direction including the intracanalicular nerve segment is in clear contrast to the dimensions of the canal in the lateral projection of the plain radiographs (PR, cephalometry). In PNF-affected, deformed mandibular rami, the cranio-caudal diameter of the canal does not necessarily differ from that of the unaffected side (10). In other words, in cases of voluminous neurogenic tumors – often accompanied by dystrophic masticatory muscles – located medially to the ramus and deforming the adjacent bone, the lesion, although thought to originate from the inferior alveolar nerve or terminal branches of the mandibular nerve, appears in many instances to respect an anatomical boundary when entering the bone. This observation has been noted repeatedly (Figure 2, Figure 3, and Figure 5) (10, 13). This assumption probably indicates currently incomplete diagnosis of NF1-associated mandibular disease due to lack of information on the nerve's composition inside the bone, incomplete imaging of the region as the basis for a hypothesis on the pathogenesis of enlarged mandibular canal in NF1, but it could also indicate the timing of tumor development and limitation

of a tumor's growth capacity in different tissues (soft tissue, bone) that may develop or grow only after the bone has completed perineural ossification (75).

Conclusion

Mandibular NF1-associated deformities are considered pathognomonic (9, 10, 38). Bone changes in the mandible of patients with NF1 occur primarily in childhood and adolescence and are considered stable throughout life (47, 48). Thus, the growth phase often appears to be the decisive factor in the interaction between tumor and bone for bone changes which follow a pattern of jaw deformities that takes on individual characteristics (14). However, exceptions to this assessment have been documented (18). In peri-mandibular PNF, there is very likely an impact of masticatory muscles on the tumor-adjacent mandibular shape (18). In this respect, the NF1 gene may also be considered a histogenesis control gene in the development of jaw dysplasia (4). Regular clinical and radiological follow-up of these patients is indicated because osseous developmental disorders can result in significant changes in jaw relations and disturbances in masticatory function (13, 58). The progression of tumors can cause extensive mandibular destruction (10, 18), and diagnostic clarification of the affected region's tumor biology is an essential task in monitoring patients (19, 62), even in cases of skull base tumors with apparently stable clinical and radiological findings.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding the publication.

Authors' Contributions

R.E. Friedrich: Treatment of the patient, conceptualization, draft and corrections of the manuscript. F. K. Kohlrusch: Literature research, draft and correction of the manuscript. C. Hagel: Histologic diagnosis, draft and corrections of

manuscript. M. Giese: Literature research, draft and correction of the manuscript. All Authors have agreed to the release of the manuscript for publication.

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