Abstract. Background: The nevoid basal cell carcinoma syndrome (NBCC) is a rare and autosomal dominant inherited disease with well-defined characteristics, summarized by Gorlin and Goltz in 1960. In the head and neck region, cerebral calcifications, basal cell carcinoma (BCC) and multiple keratocysts of the jaws are the predominant findings. The aim of this study was to determine the diagnostic findings and the therapy for patients with NBCC. Patients and Methods: The medical files of 17 patients with NBCC, treated in a single institution (females: 9, males: 8) were evaluated. Thirteen patients were also physically investigated, including X-ray diagnosis. Results: The age at the time of first surgical treatment related to the syndrome was 3 to 57 years (mean: 21.3 years). A family history for NBCC was evident for 4 patients. The number of patients with characteristic head and neck findings in the spectrum of NBCC varied: basal cell carcinoma (n=15), keratocysts of the jaws (n=13), cerebral calcification visible on plain radiographs (n=15), palmar pits (n=9). Facial dysmorphism (hypertelorism) was evident in 4, and skeletal anomalies outside the skull occurred in 10 patients. The medical histories revealed a cleft lip and palate in 2, and unilateral kidney agenesis in further 2 patients, emphasizing the variability of the syndrome. Treatment was exclusively surgical in all but 2 patients. One of these 2 patients underwent external irradiation for a BCC of the frontotemporal region. Nine years later a frontal BCC had to be treated. The other developed several other BCC inside and outside the irradiation field. Up to 50 BCC per patient had to be resected. The number of keratocysts of all patients was 66, with a predilection for the mandibular angle in 44%. On cranial computed tomograms (CCT, n=9) a number of calcifications became evident: falx (8/9), tentorium (9/9), petrosellar ligament (2/9) and carotid siphon (1/9). Cerebral cysts occurred in one third of these patients (3/9). One patient underwent surgery for a medulloblastoma during childhood. In this series of CCT of 9 patients, no cortical atrophy was found. Conclusion: The NBCC is a well-known syndrome with a variety of findings inside and outside the head and neck region. Interdisciplinary cooperation is mandatory in the diagnosis and follow-up control of patients with NBCC.

The nevoid basal cell carcinoma (NBCC) syndrome is a rare and autosomal dominant inherited disease with well-defined characteristics (1-6), summarized by Gorlin and Goltz in 1960 (synonym: Gorlin-Goltz syndrome (GGS) (7-10)). In the head and neck region, multiple basal cell carcinomas (BCC) and multiple keratocysts of the jaws are the predominant findings (11-15). In the face, the periorbital region, nose and upper lip often give rise to BCC (16). Further, cerebral calcifications in typical locations, visible on radiographs, are diagnostic for NBCC syndrome (7, 9, 17-19). The syndrome is characterized by the development of BCC in regions usually not exposed to the sunlight, like the axillary and inguinal region, elbow, or knee. According to Gorlin (7) the BCC usually develop between puberty and the 35th year of life, much earlier than in patients with BCC without a syndromatic/genetic background. Further findings in NBCC syndrome are palmar and plantar pits, skeletal anomalies (e.g. bifid ribs, hypo- or aplasia of ribs, scoliosis, shortening of metacarpalia, cyst-like lesions of long bones), calcification of the cerebral falx, and endocrine disorders (10). It was stated that the facial appearance of patients with NBCC syndrome might be pathognomonic and that macrocephalus might be a further finding (4, 18). Therapy for BCC and cysts is surgical. The aim of this study was to evaluate the surgical therapy for and the findings associated with NBCC syndrome.

Patients and Methods

The medical files of 17 patients with NBCC syndrome, treated at a single institution (females: 9, males: 8) were evaluated. Thirteen patients were re-evaluated 1 to 10 years following initial therapy. One patient was deceased, one could not be investigated due to age-
associated immobility, and two were lost at follow-up. The clinical investigation included: counting of visible skin alterations (BCC, dyskeratosis), evaluation of facial dysmorphism, a panoramic view of the jaws (all patients), and computed tomograms of the skull (9 patients).

Results

Palmoplantar pits were present in 56%. In one case an epidermoid cyst of the foot was excised (6). Keratocysts were diagnosed in 13 patients. The ratio of keratocysts arising in the mandible or maxilla was 3:2. The number of recurrences per patient and the disease-free intervals (months to years) varied considerably. Skeletal anomalies were diagnosed in 59% and clefts of the lip and palate were apparent in 2 (11.7%). Two patients had severe findings of the kidneys. Keratocysts were the initial finding in 9 patients. The results are summarized in Tables I-III.

Discussion

This report describes the high number of associated findings in NBCC syndrome, in addition to the diagnostic triad of BCC, keratocysts and cerebral calcifications. BCC were diagnosed in 14 patients. A further 2 patients, young of age, had café-au-lait spots or nevi, leaving 1 patient without cutaneous findings. This percentage of BCC in NBCC syndrome is in accordance with earlier reports (11, 16). Predominant localisations of BCC were the face, breast, back and extremities, or axillary and inguinal region, even the outer acusticus meatus (9). Keratocysts were diagnostic for NBCC syndrome in many patients, emphasizing the need for continuous medical and dental education to investigate patients with multiple keratocysts for other findings indicative of the syndrome. As two patients were young of age, the number of 13 patients (76.4%) with...
histologically proven keratocysts might increase over time. Schlien et al. (13) reported that about 50% of patients develop keratocysts before the onset of puberty. The predominance of mandibular keratocysts in females was also stressed in other reports (3:1 (7)).

Skeletal anomalies should be expected in more than 50% (9, 14). Our findings are in that range. Malformations of the rib were proposed as an early diagnostic finding for children with NBCC syndrome (20), but seem to be less frequent in larger studies (4). However, skeletal findings other than keratocysts are frequently observed in NBCC syndrome (4). We were not able to substantiate earlier judgements that the physiognomy of NBCC patients appears to be pathognomonic (4, 7, 19). A bright nasal root and/or hypertelorism was found in only 4 patients. Indeed, these findings contribute to a characteristic individual aspect, but do not constitute interrelationships.

Some reports deal with the association of NBCC syndrome and clefts of the lip, alveolus and palate (12, 15, 21-26). Van Dijk and Neering (26) reported that about 4% of NBCC patients develop a cleft lip and palate (CLP). This estimate was confirmed by recent studies (5% (8), 2.8% (4)). In this small series the incidence of CLP is much higher (11.7%). Two patients had kidney aplasia. Reports on aplastic kidneys in NBCC are very rare (3 reports: 27-29). Other kidney alterations were reported in NBCC patients: calcifications or deformities (24, 28) or cysts (12, 30). Two patients of this series had a cyst or stones of the kidneys.

Cerebral calcifications were reported as present in more than 90% (11, 12, 16). Calcification of the falx is observed regularly in the normal population, in particular in elder individuals, but with a different pattern compared to NBCC patients (7). In addition to this pathognomonic falx calcification, computed tomograms also revealed a high number of tentorial calcifications (12, 31), the latter being an even more constant CT finding. Cerebral cysts seem to contribute to the panel of findings in NBCC syndrome (32, 33). The head circumference of our patients was in the normal range. Others reported on enlarged head circumference associated with NBCC syndrome (34) and severe cerebral complications associated with this entity (24).

Table II. CCT findings in 9 patients (symbols: see legend to Table I).

<table>
<thead>
<tr>
<th>No.</th>
<th>Gender</th>
<th>Age</th>
<th>Falx calcification</th>
<th>Tentorium calcification</th>
<th>Further calcifications</th>
<th>Enlarged ventricles</th>
<th>Cerebral cyst</th>
<th>Cortical atrophy</th>
<th>Macroencephaly</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>m</td>
<td>64</td>
<td>+</td>
<td>+</td>
<td>Ligamentum petrosellare, bilateral</td>
<td>+ (adequate for age)</td>
<td>Septum pellucidum</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>f</td>
<td>31</td>
<td>+</td>
<td>+</td>
<td>Ligamentum petrosellare, bilateral</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>m</td>
<td>66</td>
<td>+</td>
<td>+</td>
<td>Carotid syphon, bilateral</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>42</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>f</td>
<td>31</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Arachnoidea</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>m</td>
<td>63</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>m</td>
<td>27</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>f</td>
<td>63</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>f</td>
<td>8</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Septum pellucidum</td>
<td>–</td>
<td>0</td>
<td>History of medulloblastoma</td>
</tr>
</tbody>
</table>

Table III. Localization and frequency of 66 jaw cysts in patients with nevoid basal cell carcinoma (NBCC) syndrome.

<table>
<thead>
<tr>
<th>Mandible</th>
<th>Maxilla</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molar and angle region</td>
<td>29 (44%)</td>
</tr>
<tr>
<td>Ramus</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Meadian and paramedian region</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Total</td>
<td>40 (60%)</td>
</tr>
</tbody>
</table>
(one case) was repeatedly reported in NBCC syndrome, in particular in young patients (4, 12, 17, 24, 37).

Conclusion

The nevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome) is an autosomal dominant inherited disease. Several findings other than the diagnostic triad of keratocysts, multiple basal cell carcinoma and cerebral calcifications might occur in these patients and cause severe complications. Interdisciplinary management is mandatory for NBCC patients. Continuous medical and in particular dental education should focus on the differential diagnosis of jaw keratocysts frequently being the first findings in young patients with NBCC syndrome (13).

References


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