Clinical study

BASAL CELL NEVUS SYNDROME. TUMOR SITES AND THERAPY
Analysis of 56 cases

B. Haferkamp, K.-J. Ernst and M. Hundeiker

ABSTRACT

In 56 patients with basal cell nevus syndrome, clinical manifestations and therapy in various tumor sites were reviewed and contrasted with data from literature. For differential diagnosis, it is essential to ascertain a complete history and to search for further symptoms of the syndrome. The most important alternatives in therapy are surgery and cryosurgery. The latter is particularly suitable in cases with large numbers of superficial basal cell carcinomas located on the trunk and extremities and for treatment during early growth stages. Cryosurgery sessions are short and the method can be employed in out-patient care, which is of special significance as basal cell nevus syndrome patients require life-long attention.

KEY WORDS

basal cell nevus syndrome, 56 patients, accompanying symptoms, tumor sites, therapy

INTRODUCTION

The basal cell nevus syndrome (BCNS, more accurate: nevoid basal cell carcinoma syndrome) is a genetically determined, polysymptomatic disease. By some authors it has therefore been labelled „fifth phacomatosis" (1). Musger (1964) (2) defined „phacomatosis" as heterogeneous alterations which are capable of progression and originate in dysplasias or early embryonic differentiation disorders. Apart from the skin, the basal cell nevus syndrome can involve to a various extent the skeletal system, the central nervous system, the eyes, and the endocrine organs. The disease shows an autosomal dominant pattern of inheritance with high penetrance and varying expressivity. The defect has recently been located to chromosome 9q in section q22-23 (3,4).

Since the close of the 19th century, cases of multiple basal cell carcinoma, osseous anomalies, mandibular cysts and retardation have been reported. Binkley and Johnson (5) described the cases of a mother and her daughter who both showed more than 1000 basal cell carcinomas and various growth defects. More publications, predominantly individual case reports, followed (6,7,8,9,10). Thies et al. (11), and a little later Gorlin and Goltz (12) identified the disease as a separate syndrome.

Characteristically, the tumor growth is initially very slow (nevoid growth stage) and becomes invasive later (oncotic growth stage) (13). It is not yet certain what causes this development. The multiple

Table 1. Age Distribution (Age at Diagnosis) of the 56 patients with basal cell nevus syndrome

Age Group	Absolute Frequency	Relative Frequency %
15 - 20 Years	5	8,9
21 - 40 Years	26	46,4
41 - 60 Years	17	30,4
61 - 80 Years	7	12,5
≥ 81 Years	1	1,8

and repetitious appearance of tumors causes difficulty in choosing an appropriate course of therapy.

The leading diagnostic criterion is the presence of multiple basal cell carcinomas. However, the first symptoms noted are often maxillary, sometimes mandibulary cysts. Additional findings in descending order of frequency are: calcification of the dura mater, dyskeratotic defects of the palms and soles, milia and epithelial cysts, malformation of the spine, and others. There is a higher-than-chance association between BCNS and other malignancies (squamous cell carcinomas of the skin, larynx and anal region; ameloblastomas; brain tumors; ovarian carcinomas; carcinomas of the mamma; renal cell carcinomas; Bowen's disease).

MATERIALS AND METHODS

In the Fachklinik Hornheide, 15,437 patients were treated for basal cell carcinoma between 1961 and 1994. Of these, 63 had been diagnosed with BCNS. Diagnosis, tumor site and treatment procedures were analysed from these patients' records. The diagnosis was accepted if any of the following criteria were met: positive family history, typical symptoms or occurrence of tumors at a young age, whereas multiple epitheliomas in arsenic patients, striated and segmentary basal cell nevi, epidermal nevi, nevoid basal cell epitheliomas of the Jablonska type, multiple basal cell carcinomas after exposition to radiation and epithelioma adenoides cysticum Brooke were ruled out in differential diagnosis. Seven patients, in whom the diagnosis of BCNS was doubtful, were not included in the evaluation.

RESULTS

1. Family History. Family history was positive in 17 (30%) of the patients. In 14 (25%), no data could be obtained from the records.

2. Distribution of Age and Sex. Among the 56 patients who were evaluated in the study 21 were males and 35 females. The diagnosis of BCNS was established as being most frequent between 21 and 40 years (Table 1), and in 30.4% of cases at an age between 41 and 60 years.

3. Accompanying Findings. The most frequently observed accompaniments were osseous anomalies and defective dentition, especially maxillomandibular cysts (38 patients, 68%, Table 2). A radiography of the maxillary region was performed in all patients except one, the skull was examined radiographically in 38 (67%) and the spine in 12 (21%) patients. Spinal involvement in the form of fused vertebrae and scoliosis was found in 9 patients (16%). Bifid, synostotic or missing ribs (4 patients, 7%) were rarely diagnosed. In 50% of the patients a calcified dura was found. Apart from basal cell carcinoma, the skin was affected mainly in the form of palmoplantar dyskeratotic defects (27%) and milia/epithelial cysts (21%). Eye involvement [hypertelorism, dystopia canthorum (4%) and motility defects (9%)] were unusual. Endocrine organs were not affected in our patients.

4. Occurrence of other Neoplasias. Of 56 patients, 13 (23%) developed other malignant tumors apart from basal cell carcinomas. Squamous cell carcinomas of the skin were found in 5 patients under the age of 50 years. Squamous cell carcinomas also appeared in the larynx and anal region. Further neoplasias were ameloblastomas, brain tumors, ovarian carcinomas, carcinomas of the mamma, renal cell carcinomas and Bowen's disease.

5. Histology of Nevoid Basal Cell Carcinomas. The histologic differentiation of basal cell carcinomas was possible in specimens of complete excisions, resections and biopsies. A large amount of superficial BCCs were treated with cryotherapy and were not evaluated. Regarding the large number of tumors treated during one session, their small size and the necessity to avoid unnecessary scarring, the requirement to verify each single tumor histologically is impossible to meet in these patients. Among the tumors that were histologically examined, solid-growing BCCs accounted for the majority (906, 52.5%). Less frequently, tumors were superficial (293, 17%) or multicentric (193, 11.2%). Other types of basal cell carcinomas (adenoid, cystic, sclerosing, keratotic, metatypical) were less common.

6. Tumor Site and Treatment. In our patients, the preferred location of basal cell carcinomas was the trunk (2457 tumors, 53.8%), followed by the face (1397 tumors, 30.6%; Table 3). In the latter area apart from other facial sites (877 tumors, 19.2%) the periorbital region and the nose were often affected. Surgical treatment was the method of choice for facial lesions, whereas basal cell carcinomas of the trunk were treated cryosurgically, especially if growing superficially. Less frequently, they were excised and very rarely irradiated. Irradiation in soft-X-ray technique was used until 1982 for the lips, ear and nose region and for the periorbital area. In other facial areas, cryotherapy has always been preferred to radiotherapy. For tumors situated on the capillitium (441, 9.7%), excisions and cryosurgery were employed in the first instance. Tumors of the extremities were rare. They were also treated cryosurgically or surgically. Radiotherapy was not used for these areas. In rare instances facial and trunk lesions were treated with 5-fluorouracil, retinoic acid and laser therapy.

DISCUSSION

The basal cell nevus syndrome presents great difficulties to the responsible doctor, partially due to diagnostic problems in cases of incomplete penetrance, partially due to choosing a therapeutic strategy for numerous and successively emerging tumors.

By no means do multiple BCCs alone give reason to suspect a basal cell nevus syndrome (14). Nevertheless, the syndrome has to be considered in cases where they appear at a young age (15). In our

Table 2. Accompanying symptoms in the 56 patients with basal cell nevus syndrome in our database (compilation as proposed by Gorlin and Sedano 1971)

Accompaniments of multiple nevoid basal cell carcinoma	Absolute Frequency	Relative Frequency %
I. Skin		
1. Palmoplantar keratinisation defects (pits)	15	27
2. Milia, epithelium cysts	12	21
3. Fibromas or neurofibromas	2	4
4. Lipomas	5	9
II. Osseous and Dental Anomalies		
1. Multiple maxillomandibular cysts	38	68
2. Ribs: bifid, synostotic, missing ribs	4	7
3. Spine: scoliosis, fusions	9	16
4. Frontal bossing	1	2
5. Progenia	0	0
6. Anomaly of the sella turcica	0	0
III. Central Nervous System		
1. Dura calcification (falx, tentorium)	28	50
2. Imbecility	1	2
3. Medulloblastoma	1	2
4. Alteration of the EEC	4	7
IV. Eyes		
1. Hypertelorism, dystopia canthorum	2	4
2. Motility disorder	5	9
3. Cataract (congenital or early onset)	0	0
4. Inhibition deformities	0	0
V. Endocrine Organs		
1. Ovarian fibroma	0	0
2. Male hypogonadism	0	0

Table 3. Choice of treatment as related to tumor site in basal cell nevus syndrome patients

Tumor Site	Absolute Frequency	Relative Frequency %	Total Absolute	Total Relative %
Capillitium			441	9.7
1. Excision	288	6.3		
2. Cryotherapy	133	2.9		
3. Soft X-ray irradiation	20	0.4		
Lips			66	1.4
1. Excision	49	1.1		
2. Cryotherapy	1			
3. Soft X-ray irradiation	16	0.3		
Eyes			255	5.6
1. Excision	216	4.7		
2. Cryotherapy	3	0.1		
3. Soft X-ray irradiation	33	0.7		
4. Interferon-alpha	3	0.1		
Ears			64	1.4
1. Excision	41	0.9		
2. Cryotherapy	9	0.2		
3. Soft X-ray irradiation	12	0.3		
4. Interferon-alpha	1			
5. 5-Fluorouracil ointment	1			
Nose			135	3.0
1. Excision	104	2.3		
2. Cryotherapy	1			
3. Soft X-ray irradiation	30	0.7		
Other Sites (Facial)			877	19.2
1. Excision	678	14.9		
2. Cryotherapy	118	2.6		
3. Soft X-ray irradiation	80	1.8		
4. Argon Laser	1			
Trunk			2457	53.8
1. Excision	462	10.1		
2. Cryotherapy	1929	42.3		
3. Soft X-ray irradiation	54	1.2		
4. 5-Fluorouracil ointment	6	0.1		
5. Retinoic acid	1			
6. Argon Laser	5	0.1		
Upper Extremity			80	1.7
1. Excision	29	0.6		
2. Cryotherapy	51	1.1		
Lower Extremitiy			190	4.2
1. Excision	40	0.9		
2. Cryotherapy	150	3.3		
Total	4565			

experience, the age of the patients at the time of diagnosis was remarkably advanced compared to data in literature. A significant proportion of the patients was between 21 and 60 years old. This may be due to the retrospective nature of the study. Treatment received in other institutions was inconsistently documented. Another reason could be the fact that the basal cell nevus syndrome shows a widely varying phenotypic expressivity: we observed a patient who developed BCCs in childhood, while other patients showed signs of the disease at an age typical for sporadic BCCs. In 1960 Thies et al. (11) indicated that abortive forms without affection of the skin can occur. They also assumed a manifestation that is not restricted to juvenile age. However, the disease is often detected late because the BCCs mimic nevi in the beginning of their development.

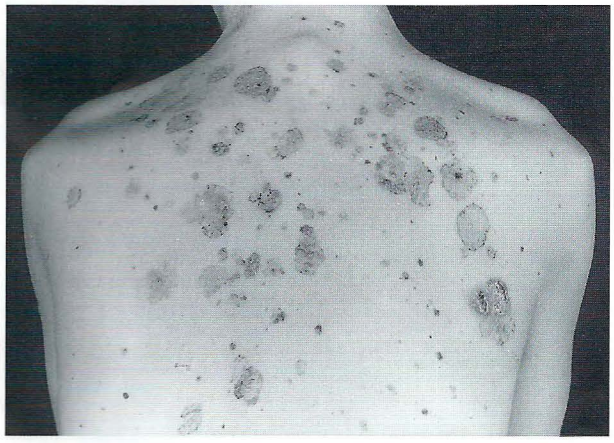
The frequency of maxillomandibular cysts (68%) in our patients is in accordance with data in literature. These cysts are considered to be the most important factor and can precede the skin affection by years. Histologically, the cysts are lined with one or more layers of squamous epithelium with a varying tendency of keratinisation. Proliferation from these cysts with the characteristics of an ameloblastoma has been reported (16). In our series there was also a patient who developed an ameloblastoma. A further sign (50%) is early calcification of the dura mater. Defects of the palms and soles, histologically focal dyskeratosis with accumulation of multi-layered basal cells, were rare in comparison to literature reports (27% vs. 50%) (17). As the palmoplantar pits are normally asymptomatic and clinically indistinct, they can easily be overlooked unless these defects are directly searched for.

In agreement with the literature in our study there is a strong association with further malignancies (23%) (18). This was similarly reported for other phacomatoses such as von Recklinghausen's or Bourneville-Pringle's disease. It can possibly be related to increased chromosomal instability (19). In one patient we observed a coincidence of basal cell nevus syndrome, neurofibromatosis and Turner's syndrome (20).

Histologically, BCCs of BCNS patients do not differ from those of the common form. The frequency distribution of the various BCC types in our excision specimens was similar to that of sporadic BCCs (21,22,23).

The distribution of sites of BCCs in BCNS differs from that of the solar-induced type (Table 3). Typically, the BCCs of basal cell nevus syndrome are not only found in continuously light-exposed areas of the skin, but also on the trunk, the capillitium and the extremities. In the patients treated in our clinic, location on the trunk clearly predominated. Facial occurrences correspond to the behaviour of sporadic BCCs, which appear mainly in the centrofacial (periorbital and nose) region. Thus, exposure to ultraviolet radiation seems to be a tumor-stimulating factor in BCNS-patients, too. Immune deficiency possibly promotes growth like it does in other tumors. Beyond that, this condition might induce the development of squamous cell carcinoma from a basal cell carcinoma (24).

The figures on tumor numbers are at the low end of the range: on the one hand, many patients are not exclusively treated in the Fachklinik Hornheide. Because of the chronicity of the disease, cooperation



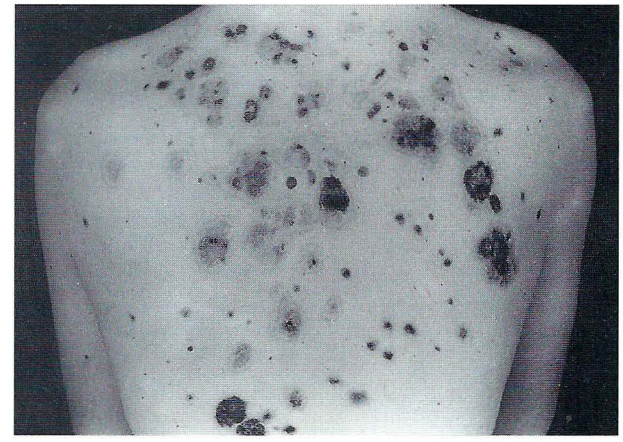


Figure 1a. Patient with basal cell nevus syndrome before cryosurgery of numerous basal cell carcinomas
Figure 1b. Patient with basal cell nevus syndrome after cryosurgery of numerous basal cell carcinomas

with other doctors is essential. On the other hand, due to their multiplicity not all of the tumours could be numerically registered. Especially the number of tumors eligible for cryosurgery often exceeded the limit in number that can possibly be documented during daily routine: occasionally, hundreds of basal cell carcinomas were treated in a single series (Fig. 1a, 1b).

Regarding the multiplicity of tumors different traemtment regimens have to be chosen. The most important treatment modalities (standard therapies) used in our clinic are surgery and cryosurgery (25). Tumor excision is indicated in cases of extended, especially facial, thick tumors, in certain histologic growth patterns (sclerosing, „savage") and in relapsing tumors. The advantage of surgical treatment is its security and the possibility of histological verification. However, one must consider that BCCs often are multicentric and appear in close vicinity of each other. In such cases they cannot be totally removed, and other methods have to be employed. Cryotherapy is best suited here (26). It is appropriate for the numerous superficial tumors on the trunk and extremities which can be detected in early stages at follow-up examinations (Fig. 2, 3). The handling is easy and treatment of multiple BCCs can be done in a short time. The method implies little inconvenience for the patient while cosmetic results are good. The disadvantages are a higher relapse-risk in cases of large deeply infiltrating tumors and prolonged wound healing. The combination of surgery and cryosurgery is possible and, in the cases listed, reasonable.

Restricted application is reseved for soft X-ray-, laser- and photodynamic therapies. Irradiation of basal cell nevus patients was employed in our clinic from 1954 to 1982. Due to the genetic pathogenesis of the disease and the risk of tumor induction, the method was abandoned. For example we observed a 14-year-old female who received radiotherapy for

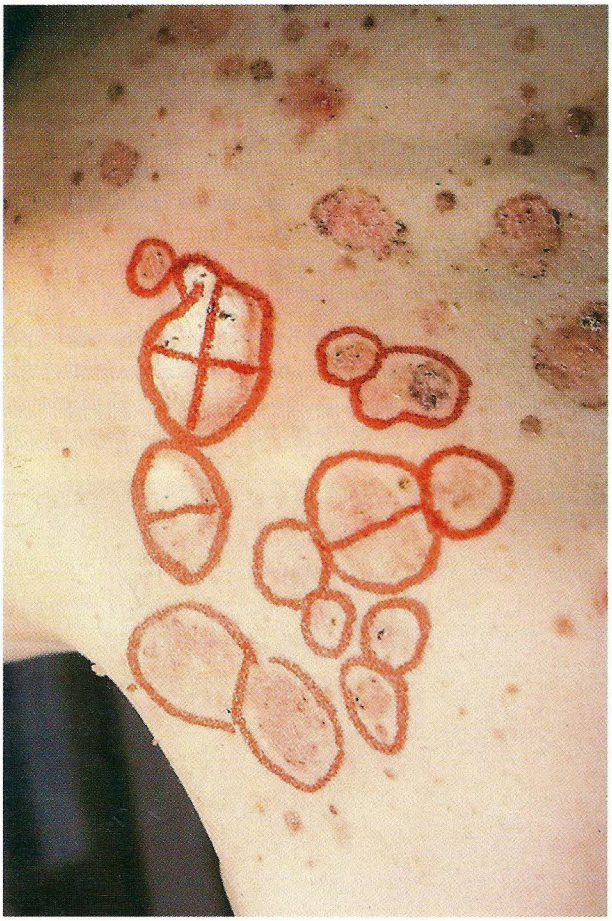


Fig. 2. Basal cell nevus syndrome. Lesions treated by cryotherapy.

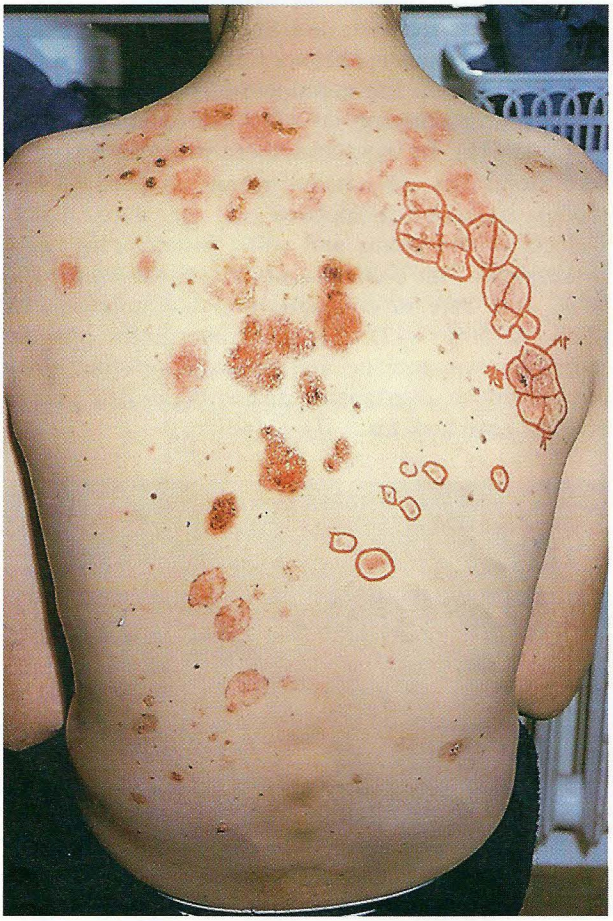


Fig. 3. Basal cell nevus syndrome. Treated lesions compared to untreated.

medulloblastoma. In consequence she developed a large number of BCCs in the exposed area (capillitium) and a few on the trunk, while the face remained unaffected. Relative indications for soft X-ray therapy are complicated tumor locations in the face and patients above the age of 60 years (27). Deeply infiltrating tumors should be treated with other methods. The skin of the trunk and extremities is more susceptible to radiogenic scarring than the face. Therefore, cryotherapy or surgery are preferable. Laser therapy is suitable only for small, demarcated tumors. For larger BCCs, the method is not safe enough. The situation is similar in regard to the recently propagated photodynamic therapy (28,29). Moreover, the method is inconvenient for the patient and cannot be recommended at this experimental stage. The same applies to interferon treatment. Infiltrations with interferon have to be continued for several weeks. They are not at all as sure to succeed as other methods. Adverse effects (fever, shivering fits, fatigue, cephalgia), though less intensive than in systemic administration, are difficult to handle (30). A good result in early superficial lesions can also be obtained with 5-fluorouracil ointment and local application of retinoids. But it has to be considered that their use is very complicated and lengthy as opposed to cryotherapy. Miltefosin in topic application is currently being tested in a multi-center study. Prevention: the most important provoking factor in this genodermatosis is ultraviolet-radiation. That´s why skin protection especially in childhood is necessary. Some authors have recommended retinoids as systemic chemopreventive agents reducing recurrences of basal-cell-carcinomas (31,32). Other authors, however, are not convinced of their efficiency. The numerous adverse effects of systemically administered retinoids, including increase in serum lipids, skin and mucosal damage and teratogenesis have to be considered (33). In summary different treatment modalities depending on localization, tumor size, side effects and patient compliance have to be considered in every case in order to achieve the best long-term result.

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AUTHORS' ADDRESSES

Birgit Haferkamp MD, Department of Dermatology, University of Wurzburg
J. Schneider-Strasse 2, 97080 Wurzburg, Germany
Klaus-Jochen Ernst MD, Department of Dermatology, Fachklinik Hornheide,
Westfalische Wilhelms Universitat, Munster, Dorbaumstrasse 300, 48157 Munster, Germany
Max Hundeiker MD, professor of dermatology, same address