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Gorlin-Goltz syndrome: clinical findings in a Italian population and review of the literature.

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Dear editor,

We have reduced the number of words as much as possible but we have added three references as recommended by the reviewers.

We have revised the manuscript according to the referees' comments and indicated the changes in red.

- We entered the abbreviation NBCCS to indicate Gorlin Goltz syndrome;
- We have included an updated reference regarding molecular findings (Gianferante DM et al. 2018) and review the test and reference list accordingly;
- We mentioned other case cohorts described in Italy;
- We changed the term "ailment shuttles";
- We changed the diagnostic criteria (Evans *DG*, Farndon *PA*. Nevoid basal cell carcinoma syndrome).
- We changed "multicenter approach" in "multidisciplinary approach";
- We changed the title.

Title: Gorlin-Goltz syndrome: clinical findings in a Italian population and review of the literature.

Contributors:

Emanuele Miraglia*[1], Alessandro Laghi[1], Chiara Iacovino[1], Antonietta Moramarco[2], Sandra Giustini[1].

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Key words: Gorlin-Goltz syndrome - Nevoid basal cell carcinoma syndrome - PTCH.

Dear editor,

Gorlin-Goltz syndrome or Nevoid basal cell carcinoma syndrome (NBCCS) is a rare inherited autosomal dominant genodermatosis, with nearly complete penetrance but variable expression. NBCCS results from mutations in the Patched 1 (*PTCH1*) gene (40%–88% of NBCCS cases with higher estimates closer to 90% in more recent studies). Recently, mutations in suppressor of fused gene (*SUFU*) and *PTCH2* have been found in patients with NBCCS. The estimated prevalence of the disease ranges between 1/57.000 and 1/256.000, with a male-to-female ratio of 1:1. The clinical features arise in the first, second, or third decades of life.[1,2]

This syndrome includes a wide spectrum of defects encompassing the skin, eyes, central nervous and endocrine system, and bones. Diagnosis is based on fulfilment of: two major diagnostic criteria and one minor diagnostic criterion or one major and three minor diagnostic criteria. Identification of a heterozygous germline PTCH1 or SUFU pathogenic variant on molecular genetic testing establishes the diagnosis if clinical features are inconclusive.[3]

In this study we sought to investigate clinical aspects in Italian patients with NBCCS. We reviewed all clinical charts of 40 NBCCS patients followed by February 1983 to February 2020 at the "Sapienza" University of Rome, Italy. All patients were investigated in a similar way with periodic evaluations that included dermatological, dental, ophthalmologic, gynecological and cardiological evaluation. Clinical examination included oral inspection, measurement of head circumference and interpupillary distance, examination of the skin for basal cell carcinomas (BCCs), and pits on the palms and soles. Radiographs of the chest, skull, spine, hands, pelvic (female) and teeth panorex were taken.

The age of patients ranged from 10 to 85 years, with a mean of 36.4 years. The follow-up period ranged from 1 to 30 years. Twenty-one (52.5%) were female, and 19 (47.5%) were male. A family history of NBCCS was present in 9/40 (22.5%) patients. Of 40 patients, 24 underwent genetic testing for PTCH1. Of the 24 patients tested, 13 (54.1%) were found to have a pathogenic PTCH1 mutation. BCCs were present in 87.5% of the patients (80% of the BCCs were located in UV-

exposed areas). The majority of the histologically examined BCCs were nodular. Palmar or plantar pitting was present in 60.7% of the patients. A calcification of the falx cerebri was found in 72.5% of the patients while odontogenic keratocysts (OKCs) were present in 67.5%. Ocular manifestations were present in 85% of the patients (hypertelorism, strabismus, epiretinal membranes, congenital cataract, nystagmus, colobomas and myelinated optic nerve fiber layers). Other features were: macrocephaly (67.5%), scoliosis (35%), rib anomalie (22.5%) and syndactyly (2.5%). Of the 21 female patients, 47.5% had ovarian fibromas. In our patient cohort there was no medulloblastoma (Table 1).

The common manifestations in NBCCS are BCCs, OKCs of the jaw, congenital skeletal anomalies, palmar pits, and intracranial ectopic calcifications of the falx cerebri. More than 100 less common features have been identified. Multiple BCCs with early onset represent the most frequent clinical manifestation (75% patients >20 years old and 90% patients >40 years old). In patients with NBCCS, BCCs are more likely to be multiple lesions, polymorphic in nature, in either sex, and even areas not exposed to sunlight can be affected. They are not histologically different, but show a higher rate of recurrence after treatment than in non-syndrome patients. Palmar or plantar pits (overall prevalence varies from 70% to 90%) are caused by a partial or complete absence of the corneum. They have a diameter of 2-3 mm and a depth of 1-3 mm. OKCs are rare benign neoplasms of the jaw with a 65% to 75% prevalence. They are generally found incidentally as a result of radiologic examinations and may be the first sign of the syndrome. Lamellar calcification of the falx cerebri is the most common radiological manifestation with a prevalence between 70% and 92%; this calcification is not found in early childhood. Medulloblastoma, particularly the desmoplastic variant occurring in early childhood, is diagnosed in 5% of NBCCS. Other features of the syndrome include craniofacial anomalies, skeletal anomalies, neurologic or central nervous system anomalies and other anomalies including genitourinary tract, cardiac and ophthalmologic anomalies. Tendency to tumors may be observed.

This study was performed to delineate phenotypic characterization in patients with NBCCS. Four major studies investigated the clinical presentations of NBCCS. These studies were performed on populations in Japan,[4] Australia,[5] UK,[6] and USA.[7] Some studies have also been conducted in Italy in smaller populations.[8] The most significant finding of this study was the high frequency of BCCs and ovarian fibroma (Table 1).

To our knowledge, it represents the largest Italian study and one of the largest NBCCS cohorts published to date. In our case, unlike the other studies, all patients underwent multispecialist visits and instrumental investigations, in a similar way, in one center, every 3-6 months obtaining more precise and accurate data.

A multidisciplinary approach is necessary in the diagnosis and treatment in patients with NBCCS. Early diagnosis may allow patients to receive conservative treatment instead of complex therapies and render other family members aware of potential genetic risks.

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Patients N.	40	84	105	118	157
BCCs	87.5%	47%	80%	76%	37.8%
Calcification of falx cerebri	72.5%	not assessed	65%	92%	79.6%
OKCs of the jaw	67.5%	66%	74%	75%	86.3%
Macrocephaly	67.5%	not assessed	49.2%	80%	26.5%
Pitting	60.7%	71%	87%	80%	60.1%
Ovarian fibroma	47.5%	24%	17%	14%	12.5%
Hypertelorism	47.5%	not assessed	not assessed	6%	68.8%
Scoliosis	32.5%	not assessed	31%	not assessed	not assessed
Rib anomalie	22.5%	not assessed	38%	45%	36.4%
Syndactyly	2.5%	not assessed	0%	3%	2.1%
Medulloblastoma	0%	4%	4%	1%	3.3%

Table I. Comparison of clinical manifestations of the NBCCS.

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