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CONFERENCE REPORT

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Consensus Statement From the First International Colloquium on Basal Cell Nevus Syndrome (BCNS)

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The first international colloquium on basal cell nevus syndrome (BCNS) was held at Saint Louis University School of Medicine and supported by the Basal Cell Carcinoma Nevus Syndrome (BCCNS) Life Support Network (www.gorlinsyndrome.org). The foremost goal of the conference was to review and revise the prior diagnostic criteria and define the surveillance recommendations for affected pediatric and adult patients to allow for early intervention. The invited consensus group participants included geneticists, dermatologists, orthopedists, neurologists, and dental/oral medicine specialists, who treat patients with BCNS or related disorders. This group also included individuals who have a research interest in BCNS and who additionally serve on the medical advisory board of the BCCNS Life Support Network. Expert opinion was based on the collective clinical and research experience of the consensus group participants after presentation and review of the previously published literature regarding diagnosis and treatment of BCNS. A consensus was achieved and agreed upon by open roundtable discussion of the group participants. The consensus statement outlines the proposed diagnostic and management protocols that will hopefully limit morbidity and mortality for affected individuals until more specific and targeted therapies are widely available.

Key words: basal cell nevus syndrome; nevoid basal cell carcinoma syndrome; basal cell carcinoma nevus syndrome; Gorlin syndrome; Gorlin–Goltz syndrome; odontogenic cysts; basal cell carcinoma; medulloblastoma; primitive neuroectodermal tumor; hereditary neoplastic syndromes; developmental bone diseases; genodermatoses

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INTRODUCTION

Background

Basal cell nevus syndrome (BCNS, OMIM #109400), also known as nevoid basal cell carcinoma syndrome (NBCCS), basal cell carcinoma nevus syndrome (BCCNS), Gorlin syndrome, and Gorlin–Goltz syndrome, is a autosomal dominant inherited syndrome that predisposes to overgrowth and tumor formation, namely basal cell carcinomas, odontogenic keratocysts, as well as skeletal anomalies. Characteristic bony changes consistent with this syndrome were noted in two Egyptian skeletons from the Dynastic Period (3000–2575 BC) [Santinoff and Wells, 1969] but it was first described as an autosomal dominant syndrome in 1960 by Dr. Gorlin and Dr. Goltz in a family with basal cell carcinomas, jaw cysts, and bifid ribs [Gorlin and Goltz, 1960]. Since that time, over 1,000 manuscripts related to this syndrome have been published with an incidence reported as high as 1 in 19,000 births [Jones et al., 2011]. The clinical and radiologic findings have been further characterized and diagnostic criteria established [Evans et al., 1993; Shanley et al., 1994; Kimonis et al., 1997; Kimonis et al., 2004]. As well, the genetic basis of the syndrome was identified with causative mutations in several genes in the sonic hedgehog signaling pathway, including PTCH1 [Hahn et al., 1996; Johnson et al., 1996], PTCH2 [Fan et al., 2008], and SUFU [Pastorino et al., 2009]. Genotype–phenotype correlations are not evident and a great deal of variability in presentation has been noted [Bale, 1997; Wicking et al., 1997]. This heterogeneity, along with the relative rarity of the syndrome, can lead to delayed diagnosis and subsequent treatments that greatly increase the associated morbidity and even mortality.

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MATERIALS AND METHODS

Objectives

With the over-arching goal of developing protocols for early intervention, the BCCNS Life Support Network convened the first international BCNS colloquium. This conference was hosted by Saint Louis University Department of Dermatology and the Saint Louis University Cancer Center on May 2–3, 2005. It attracted 55 affected patients, their families, and medical, dental, and research experts from around the country and internationally.

The aims of the conference were to better define the physical findings associated with BCNS through multidisciplinary evaluations, to obtain tissue including blood and skin samples for further research, to scientifically present and discuss the current literature on BCNS, and to review and revise the prior diagnostic criteria for this syndrome, as well as define the surveillance recommendations for these patients with the goal of early intervention to decrease morbidity and mortality.

Participants

The faculty for the presentations and the roundtable discussion were invited by the BCCNS Life Support Network based on their medical, dental, and research expertise of the syndrome. Additional faculty and medical personnel from the sponsoring institution performed clinical evaluations and also provided medical expertise related to their specialty areas, including dermatology, genetics, ophthalmology, orthopedics, neurology, audiology, and developmental-behavioral health. The meetings were open and the conference was designed to update physicians in dermatology, oral and maxillofacial surgery, oral pathology, dentistry, genetics, neurology, pediatrics, family practice, and internal medicine, as well as other health care providers, on issues related to the diagnosis and management of BCNS. There were 15 invited faculty members who composed the consensus group and who were responsible for developing updated diagnostic and surveillance protocols (Appendix I). The BCCNS Family Support Network provided travel funding for this conference and Saint Louis University provided personnel and facilities support as well as processing of collected specimens.

Evidence

On the first day of the conference, subspecialty literature reviews, including dermatology, oncology, genetics, molecular genetics, radiology, otolaryngology, oral pathology, neurology, and development, were presented to the group by the faculty members. These presentations included clinical features, diagnostic criteria, treatment modalities, management strategies, and research opportunities. Patient evaluations by the clinicians followed. The second day included a preliminary review of the survey data, panel discussions with BCNS affected individuals and a roundtable discussion to develop updated protocols for diagnosis and surveillance of BCNS.

RESULTS

Consensus Process

The consensus recommendations are derived from specific questions posed to the consensus group during a roundtable discussion. The recommendations are based on the collective clinical and research expertise of the faculty participants who had reviewed the questions and the current body of literature in their specialty areas prior to providing their opinions to the group discussion.

(1) Can we agree on an internationally recognized name?

It was determined that an internationally recognized name for consistency in the medical literature was desirable, but this was felt to be outside of the group's purview and left for the various patient support groups to determine.

(2) Do the diagnostic criteria need to be revisited?

The current diagnostic criteria and definition of the disease were discussed. There have been several studies that have defined the clinical and radiologic characteristics of BCNS [Evans et al., 1993; Shanley et al., 1994; Kimonis et al., 1997; Kimonis et al., 2004]. From this, diagnostic criteria have been proposed and vary by source, but there have been no studies to define the sensitivity and specificity of which phenotypic combination is most accurate for diagnosis [Evans and Farndon, 2002].

While consensus could not be reached for a formal recommendation on the diagnostic criteria, it was decided that a suspected diagnosis of BCNS could be reasonably considered based on the findings of less stringent criteria of: (1) one major criterion and molecular confirmation; (2) two major criteria; or (3) one major and two minor criteria. It was additionally discussed that medulloblastoma (also known as primitive neuroectodermal tumor) should be considered a major, and not a minor, criterion as this may lead to increased early detection if recognized as a potential indicator of an underlying syndrome, since it typically manifests in children 2 years of age and younger. Therefore, the major criteria for diagnosis would include: (1) BCC prior to 20 years old or excessive numbers of BCCs out of proportion to prior sun exposure and skin type; (2) odontogenic keratocyst of the jaw prior to 20 years of age; (3) palmar or plantar pitting; (4) lamellar calcification of the falx cerebri; (5) medulloblastoma, typically desmoplastic; (6) first degree relative with BCNS. The minor criteria would then include (1) rib anomalies; (2) other specific skeletal malformations and radiologic changes (i.e., vertebral anomolies, kyphoscoliosis, short fourth metacarpals, postaxial polydactyly); (3) macrocephaly; (4) cleft/lip palate; (5) ovarian/cardiac fibroma; (6) lymphomesenteric cysts; (7) ocular abnormalities (i.e., strabismus, hypertelorism, congenital cataracts, glaucoma, coloboma).

(3) What are the recommendations for genetic testing?

It was determined that the clinical criteria are quite good in establishing a suspected diagnosis and that molecular-genetic confirmation is not warranted in all cases. The positive mutation detection rate of sequence analysis for PTCH1 is approximately 75% in patients meeting clinical criteria, but has been reported as low as 60% [Jones et al., 2011]. Although genetic testing is considered the gold standard for diagnosis, it is also very expensive and can be cost prohibitive. It was determined that genetic testing for

PTCH1, which is the most common mutation, is warranted in the following clinical scenarios, as the results may impact diagnosis and management within an individual or a family: (1) Prenatal testing if known familial mutation. (2) Confirmatory diagnosis in patients with some clinical signs but not meeting criteria as this would allow for increased surveillance and improved patient care outcomes. (3) Predictive testing for patients with an affected family member who is at risk but does not met clinical criteria.

(4) What are the criteria for evaluation or ''triggers'' for screening?

The discussion regarding this issue centered on the fact that many of the patients had one or more early clinical signs suggestive of BCNS but many were not diagnosed until adulthood. Therefore, certain signs were considered ''triggers'' which should result in diagnostic evaluation as per the recommended diagnostic protocol (Table I). These triggers were: (1) Odontogenic keratocysts in children <20 years of age. It was noted that inaccuracy in histologic diagnosis is common among oral pathologists and that review by an oral pathologist with expertise would ensure the very specific microscopic features were appreciated for accurate diagnosis. (2) BCC in persons <20 years of age. (3) Palmar or plantar pits. (4) Lamellar calcification of the falx cerebri. (5) Medullobastoma with desmoplastic histology in combination with any of the other major or minor criteria.

(5) Where should efforts be concentrated for educating physicians about BCNS?

It was felt that dermatologists and geneticists are fairly familiar with this syndrome but that other physician groups may not be as

TABLE I. The Diagnostic Protocol for Evaluation of Patients With Suspected BCNS

- Medical history to include:
  - Birth history to include: macrocephaly, hydrocephalus, undescended testes, hernia
  - Developmental history to include: achievement of developmental milestones, school performance, height and weight as compared to siblings
  - Medical/surgical history to include: history/treatment of brain tumor, history/treatment of strabismus, oral cleft repair, dental extractions or oral surgery, surgical treatment of skin lesions, cardiac problems, infertility, fractures
  - Social history to include: environmental exposure, including radiation therapy, ultraviolet exposure
- Examination by a medical/clinical geneticist to include:
  - Facial dysmorphology including:
    - Macrocephaly, biparietal/frontal bossing, broad nasal root, mandibular prognathism, facial asymmetry
    - Oral clefting, dental malocclusion
    - Hypertelorism, synophrys, coloboma, epicanthal folds
  - Skeletal exam for pectus anomalies, Sprengel deformity, scoliosis
  - Skin exam for pits of soles (especially the arch), palms, webspaces between fingers
  - Inguinal hernia
- Radiologic exam to include:
  - Panorex of jaw (digital if possible)
  - MRI of brain
  - Additional studies if warranted (digital if possible)
    - PA and lateral skull for ectopic calcification
    - CXR for evaluation of bifid ribs
    - Full PA and lateral spine for scoliosis and vertebral anomolies
    - Long bones for bone cysts
    - Hand film for flame-shaped (Dunnick's) lucencies of phalanges
- Dermatologic exam to include:
  - Full skin exam to assess for:
    - Palmar/plantar pits
    - Basal cell carcinomas (which can be atypical in presentation)
    - Milia-like papules in the periorbital and perinasal area
    - Radiation port site if prior radiation
    - Dermoid cysts especially at the web space of the 1st and 2nd fingers
- Dental exam to include:
  - Digital panorex of jaw if not previously done
  - Sinus films if symptomatic
- Cardiology exam to include:
  - Cardiac ultrasound
- Gynecology exam to include:
  - Pelvic ultrasound

attuned to this diagnosis. This lack of awareness can then lead to delayed diagnosis when the early clinical signs are not recognized. Groups that may benefit from increased education regarding this condition would include neurosurgeons who are more likely to encounter patients with medulloblastoma, gynecologists who are more likely to see patients with ovarian fibromas and radiologists who are more likely to find the skeletal abnormalities and calcification of the falx on routine radiographs.

(6) What changes to the surveillance protocol for pediatric patients with BCNS should be considered (see Table II)?

It was felt that all pediatric patients with BCNS should be followed by a medical geneticist with an annual genetics evaluation to ensure that all multidisciplinary issues are being addressed and appropriate referrals are being made. Dermatology examination was recommended yearly or every 6 months after developing the first BCC. The recommendation for Panorex of the jaw was changed to reflect the availability of new technology. Therefore, Panorex should be done utilizing digital imaging with 6 in. film starting at age three or as soon as tolerated. Evaluation for scoliosis was added with recommendations to be screened at 1 year of age or at time of diagnosis. If an abnormality is detected, repeat with scoliosis protocol every 6 months or sooner as required for progression. Recommendation for routine developmental screening to include vision, hearing, and speech screening with well child visits was also added. For patients failing the routine screening, not meeting developmental milestones or with difficulty learning in school, more extensive assessment would be warranted. Initial psychological evaluation was additionally recommended for support and counseling for this chronic condition and then as warranted based on the individual's situation. Baseline cardiac ultrasound was considered to be a reasonable, non-invasive test to rule out a potentially life-threatening cardiac fibroma; although it was felt to be of potentially low yield. Pelvic ultrasound for menarchal girls and annual ophthalmologic exam were felt to be

TABLE II. Management Protocol for Surveillance of Pediatric Patients With BCNS

Baseline MRI of brain with contrast and epilepsy protocol
Repeat yearly until 8 years old, then discontinue
Repeat sooner if symptomatic
Baseline cardiac ultrasound
Repeat if symptomatic
Baseline dermatologic examination
Repeat yearly until first BCC
After first BCC, repeat every 6 months or more frequently as needed
Baseline digital panorex of jaw (as soon as tolerated)
Repeat yearly until first jaw cyst
After first jaw cyst, repeat every 6 months until no jaw cysts for 2 years or until age 21
Repeat more regularly if needed for symptoms or occurrence
Baseline spine film at age 1 or at time of diagnosis (digital if possible)
Repeat if symptomatic
If abnormal, repeat per scoliosis protocol every 6 months
Pelvis ultrasound in girls at menarche or age 18
Sooner if symptomatic
Repeat if abnormal or if symptoms develop
Routine developmental screening with well child visits
If fails screening or if not meeting milestones, further developmental assessment and testing is warranted
If school age with difficulty learning in school, cognitive evaluation and testing is warranted
Annual vision, hearing, and speech screenings
Continue through school age
Baseline ophthalmology evaluation
Repeat if symptomatic
Initial psychological evaluation
To establish a relationship for support and counseling
Follow-up would be based on individual recommendations from the initial evaluation
Baseline medical/clinical genetics evaluation
Repeat annually to ensure multidisciplinary care recommendations are being followed
Molecular diagnosis
If necessary to confirm diagnosis
Minimize ionizing radiation exposure and maximize protection
Radiographs warranted for evaluation of valid medical problems
Utilize non-ionizing/digital imaging modalities if possible

TABLE III. Management Protocol for Surveillance of Adult Patients With BCNS

- Baseline MRI of brain with contrast and epilepsy protocol if not done previously
  - For comparison if symptoms develop in the future
  - Repeated as needed for symptoms
- Full skin examination by a dermatologist every 4 months
  - More frequently if new skin lesions present at each exam
- Digital panorex of jaw annually
  - Repeat as needed for symptoms
- Medical/clinical genetics evaluation annually
  - Molecular diagnosis if indicated
- Genetic counseling at baseline
  - Preconception/prenatal counseling for couples at risk
- Psychological evaluation as needed for support and counseling
  - Repeat as individually needed
- Neurology evaluation annually if prior medulloblastoma
  - Repeat as needed for symptoms
- Obstetrics—gynecology evaluation annually for female patients
  - Repeat as needed for symptoms
    - Pelvic ultrasound at baseline and if symptomatic
  - Preconception/prenatal counseling for couples at risk
  - Maternal fetal medicine evaluation for at risk pregnancies
    - Assessment of fetus for cardiac fibromas, hydrocephalus and macrocephaly
- Nutritional assessment to include Vitamin A, B, C, and D levels on an annual basis
- Minimize ionizing radiation exposure and maximize protection
  - Radiographs appropriate for valid medical problems
  - Utilize non-ionizing/digital imaging modalities if possible

important but consensus was not reached regarding a formal recommendation.

(7) What changes should be considered to the surveillance protocol for adult patients with BCNS (see Table III)?

Baseline CT of the brain was changed to baseline MRI, if not done at age 8 or later. Dermatologic full skin exams were changed to a minimum of every 4 months or more frequently at the discretion of the treating dermatologist based on an individual patient's history. The Panorex was also changed to digital Panorex with 6 in. film yearly, but more frequently for regular cyst occurrence or less frequently if large number of facial BCCs or increased concern for radiation exposure.

(8) What additional recommendations are important regarding the care of patients with BCNS?

Patients who are postcraniospinal radiation should have an annual neurological assessment for the possible development of meningioma. It is also prudent to limit the amount of any type of radiation for these patients. It is therefore advised that radiographs, including skull film or chest X-ray, to assess for major or minor criteria not be performed unless the diagnosis is in question or it is clinically indicated for management of the patient for valid medical issues. If necessary, modalities utilizing non-ionizing radiation, such as MRI, ultrasound, or digital technology, are preferred.

(9) What are areas of research that would be important to pursue?

In regards to clinical questions, evaluation of cardiac issues and recommended surveillance was felt to be an important area for study. In addition, the gynecologic issues and need for evaluation are also not well characterized and would benefit from further study. Specific targeted therapies, as well as chemopreventative agents, are vitally needed to reduce the morbidity of the available treatment modalities that often lead to pain, scarring, and disfigurement. A patient registry to allow for improved clinical characterization and assessment of the diagnostic criteria, as well as to assist in identifying individuals for future clinical and therapeutic studies, was felt to be a beneficial project worth pursuing. In addition, it was suggested that improvements to the BCCNS Life Support Network website would also be helpful for education of its families and the medical and dental communities, to include templates for insurance letters, guidelines for diagnosis and management, as well as subspecialty diagnostic modules, including dermatology, neurology, gynecology, ophthalmology, genetics, psychology, developmental health, and radiology.

DISCUSSION

Conclusion

BCNS is an uncommon but important entity to recognize so that appropriate diagnostic studies can be undertaken (see Table I). Once a diagnosis is confirmed, either on a clinical or molecular basis, it is vital for the patient to be appropriately managed per the surveillance protocols proposed by the consensus group (see Tables II and III). Adhering to these protocols will hopefully limit morbidity and mortality for affected individuals until more specific and targeted therapies are widely available.

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APPENDIX

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