Medullated Nerve Fibers

A Sign of Multiple Basal Cell Nevus (Gorlin's) Syndrome

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- Four patients had Gorlin's (or basal cell nevus) syndrome and pronounced medullated nerve fibers. The medullation is an additional ophthalmic manifestation of Gorlin's syndrome, which is autosomal-dominant and noted for its variable expressivity.

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The multiple basal cell nevi (Gorlin's) syndrome is inherited as an autosomal-dominant trait with marked penetrance and variable expressivity. This syndrome is named after Robert J. Gorlin, who, with Robert W. Goltz, first gave an extensive overview of the literature in 1960 when they recognized the association between the major manifestations of the syndrome: multiple nevoid basal cell carcinomas starting at an early age, jaw cysts, and bifid rib. Subsequently, many authors, emphasizing the variable expressivity of Gorlin's syndrome, have described additional anomalies that may affect almost any system of the body, including the skin, the skeleton, the endocrine and neurologic systems, and the eye and ear. Ectopic calcification, especially of the falx cerebri, is an almost constant feature. The most common ophthalmologic signs, aside from palpebral basal cell carcinoma, are squint and hypertelorism.

This report describes four white patients with Gorlin's syndrome who have prominent medullated retinal nerve fibers, which we present as an additional feature of the syndrome. Literature research revealed four more patients with Gorlin's syndrome and medullated nerve fibers.

REPORT OF CASES

Of our four patients, the ophthalmic signs and symptoms are given in the Table.

The signs mentioned below in the case reports are pertinent to Gorlin's syndrome unless otherwise stated.

CASE 1.—A 32-year-old woman was referred to the Rotterdam (the Netherlands) Eye Clinic to discover if a fundus abnormality in her right eye was associated with Gorlin's syndrome. She had had

| Ophthalmic Signs and Symptoms in Four Cases of Gorlin's Syndrome* |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                             | Case 1                     | Case 2                     | Case 3                     |
| Age, yr/sex                 | 32/F                       | 30/M                       | 45/M                       | 49/M                       |
| Palpebral carcinoma         | −                          | R+ L+                      | R+ L+                      | R− L+                      |
| Squint                      | R exotropia 45°            | −                          | L esotropia 10° after surgery | R to alternating exotropia 15° |
| Visual acuity and refraction| R 1.60 Sph; L 0.8 Sph 0.50 | R 0.85 E; L 1.6 C + 0.50 | R 0.56 E; L 1.60 | R 1.0 E; L 1.0 E |
| Meibomian cysts             | −                          | +                          | −                          | −                          |
| Nystagmus                   | −                          | Second degree rotatory counterclockwise | Horizontal pendular | −                          |
| Medullated nerve fibers     | R+ L−                      | R+ L+                      | R+ L+                      | R− L+                      |
| Visual fields               | R relative central scotoma; L normal | R enlarged blind spot; L enlarged blind spot | Refused | R normal; L corresponding relative scotoma |
| Electro-oculogram           | R and L normal             | R and L normal             | Not done                   | Refused                    |
| Electroretinogram           | R and L normal             | R and L normal             | R and L normal             | R and L normal             |
| Pattern visually evoked cortical potentials | R lowered amplitude delayed response, L normal | R and L normal | R and L normal |
| Additional signs not connected with syndrome | Heterochromia iridium; R yellow lower than L; free floating pearl in R vitreous; fluffy ball in L vitreous; R 20 mm, L 16 mm exophthalmus | L chemosis; L facial paresis | L Marcus-Gunn pupil; L inferior retinoschisis; L telangiectasis; L posterior subcapsular cataract | Pigment epithelial atrophy under medullated fibers |
| Macular pucker              | R+ L−                      | R+ L+                      | R− L?                      | R− L+                      |

*All patients had hypertelorism: R indicates right eye; L, left eye; E, emmetropic; plus sign, present; Sph, spherical correction; C, cylindrical correction; minus sign, absent; question mark, unknown.
poor visual acuity in her right eye as long as she could remember. At the age of 3 years, she had to wear eyeglasses, and until her ninth year, she had occlusion therapy. From the age of 9 years onward she had repeatedly been operated on for jaw cysts. In 1962 a basal cell carcinoma was removed from below her left clavicle; in 1984 a fibroma was removed from her back. Also, a temporal blepharorraphy was done because of protrusion of both eyes. Her uterus and ovaries had been removed in 1983 as a result of cysts in her oviducts. On several occasions she had been examined by a neurologist for headaches. A computed tomographic scan in 1983 showed extensive calcification of the falk cerebi and tentorium cerebelli. Her height was 1.87 cm. The orthopedic surgeon found cervical scoliosis, spina bifida occulta, and bradymetacarpalia 4 and 5 in both hands. Skeletal scintigraphy showed spots in both knees, right femur, sacroiliac joints, chin, right upper jaw, and right and left frontoparietal area. In the right fundus (Fig 1) we found medullated nerve fibers, tortuosity of the vessels, fibrosis of the internal limiting membrane with a hole in this fibrotic layer, and a small, slightly elevated tumor just below the fovea. This tumor appeared to be slightly whiter than the medullated nerve fibers. The family history revealed that her mother had received a hip prosthesis at the age of 59 years and that her brother was amblyopic because of right esotropia. No further investigation was possible, so it is unclear whether they too were afflicted.

**Case 2.**—Two years earlier, a 28-year-old man with jaw cysts, medullated nerve fibers, and a long history of multiple basal cell carcinoma had been seen in Rotterdam. Some carcinomas had been removed surgically and some treated by radiotherapy and etretinate (Tigason), an aromatic retinoid. He had frontal and parietalbossing. On reexamination we found a nystagmus and left-sided facial paresis. He was slightly mentally retarded; therefore he neglected to tell us that he had had a neurosurgical operation as a child. By coincidence, however, we found a fundus picture that was the same as the one of his right eye (Fig 2, left) in an article by Hermans et al. From this article, in which he was case 2, we learned that he was born by cesarean section as the youngest of six children, one of whom had a cleft palate. He showed retarded development, and at the age of 4 years he was operated on for a medulloblastoma; this was followed by radiotherapy. Two years later basal cell nevi started to grow. He was then examined twice by an ophthalmologist (in 1961 and 1963) because Hermans et al considered Gorlin's syndrome to be a fifth phakomatosis. The ophthalmologist described a rather high swelling at the margin of the right disc with medullated nerve fibers.
but on both occasions no abnormalities were found in his left eye. He now had a small, round patch of medullated nerve fibers in his left eye too (Fig 2, right). In 1962 a cyst was removed from his left maxillary sinus. Also, a bifid rib and thoracic scoliosis were found. A neurologic examination was performed because of the nystagmus and facial paresis. The ensuing computed tomographic scan in April 1985 showed an old occipital trepanation, a calcified round structure on the left side next to the fourth ventricle, calcification of the falx cerebri and tentorium cerebelli, and a cyst in the left maxillary sinus.

CASE 3.—A 45-year-old man was seen at Moorfields Eye Hospital, London. He had multiple basal cell carcinomas on his scalp, face, and trunk since the age of 26 years; he also had bifid right upper rib, jaw cysts, and intracranial calcification of the falx cerebri and pituitary fossa. His father required surgery for multiple facial skin lesions, for which the histologic findings are unknown. The family history is otherwise negative. A thick band of medullated nerve fibers radiated from the right optic disc along the inferior temporal arcade (Fig 3). Thick medullated nerve fibers ran in all directions from the left disc. Due to the cataract in his left eye no clear pictures could be obtained.

CASE 4.—A 49-year-old man had multiple basal cell carcinomas on his trunk and eyelids, first noted at the age of 37 years. He had multiple jaw cysts and prorokeratosis of Mantoux on his palms. Two of his four children were also affected by Gorlin's syndrome. Medullated nerve fibers were present on the left superior temporal arcade (Fig 4, left) with an underlying atrophic area. A macular pucker with fine retinal folds was visible in the same eye. The fluorescein angiogram showed no choriocapillary layer in the atrophic area (Fig 4, right); no leakage was present from the vessels in the pucker.

**COMMENT**

More than 334 cases of Gorlin's syndrome have been published to date in 88 reports. Most patients had multiple basal cell carcinomas, but some kindreds have been described in which few skin lesions have been found. Our first case fits this category. This patient had had only one basal cell carcinoma and one fibroma. Fibromas arise in these patients in many tissues, including skin, breast, uterus, ovary, and often precede the appearance of the basal cell carcinomas. Cases 1 through 3 had the major manifestations of the disorder. We had no opportunity to examine the family members of the first three patients, although the father of patient 3 was probably affected. Patient 4 had an established family history of the disorder.

Duke-Elder mentioned that medullated nerve fibers are estimated to occur in three to six per thousand ophthalmic patients. More recently (1981), 0.98% of 3,968 consecutive
Autopsy cases were found to have medullated nerve fibers, and in only three cases (0.75 per thousand) were they present in both eyes. Two of our patients had bilateral medullated nerve fibers and we consider it likely that these fibers are more than a coincidental connection with Gorlin's syndrome. Search of the literature uncovered case reports of three more patients with this combination, while a fourth report showed a fundus picture resembling medullated nerve fibers. Gorlin's syndrome has its manifestations in different systems of the body. From many literature reports, it seems that an ophthalmologist was never consulted so the incidence of ophthalmic abnormalities may be much higher than reported.

From an extensive literature search we conclude that eyelid carcinomas, hypertelorism, and squint are the most common findings. Meibomian cysts or nystagmus are less frequently mentioned. Optic colobomas, glaucoma, and retinal atrophy, however, are rare, but these are often cited because they were reported in the first report by Gorlin and Goltz. Also, we found retinoschisis and macular pucker mentioned only once.

The small tumor below the fovea noted in case 1 seems atypical to the normal pattern of the arcuate fibers. This may be due to the more often encountered contraction of the internal limiting membrane in eyes with medullated fibers (A. Wessing, MD, oral communication, May 18, 1985). It is remarkable that patients 1, 2, and 4 had a macular pucker while the cataract in the left eye of patient 3 made evaluation of the macular area impossible. Straatsma et al. did not mention any macular pucker in 42 eyes from autopsy cases and in 37 eyes of living patients with medullated nerve fibers. They did mention, however, amblyopia concomitant with this disorder, and it is hard to tell whether patients 1 and 3 had poor visual acuity in one eye because of strabismic amblyopia or medullated fibers. Myelination of the optic nerve fibers may normally continue until after the age of 5 years, and there have been several reports on progressive myelination of retinal nerve fibers thereafter. We could not obtain reliable data on the age at which the squint of patients 1 and 3 started so the cause is uncertain. We are, however, fairly sure about the development of the myelinated fibers in the left eye of patient 2 after his eighth year of life because of the importance Hermans et al. put on the ophthalmologic signs. We contacted the ophthalmologist but unfortunately he no longer had pictures of the left fundus.

We performed electrophysiologic studies in patients 1 and 2 because of the often-mentioned retinal degeneration. We could find, however, only one report of a combination of Gorlin's syndrome and tapetoretinal degeneration, 11,12 so we did not stress this point, as patient 4 refused these investigations. Patient 3 was unavailable for follow-up. The lowered responses in the pattern visually evoked cortical potentials of the right eye of patient 1 are accounted for by the poor visual acuity in that eye.

Other multisystem congenital disorders have been associated with medullated nerve fibers. An increased frequency of association has been reported between medullated nerve fibers and the cranial dysostoses. 11,12 Frontal bossing with hypertelorism is one type of dysostosis that is often encountered in Gorlin's syndrome. 11,12 On biomicroscopy the small tumor in patient 1 and the medullated fibers in the right and left eye of patient 2 were slightly prominent and might also partly be astrocytomas. Astrocytomas are known to occur in neurofibromatosis in which medullated nerve fibers are also described.

These four cases highlight the occurrence of nerve fiber medullation as a further ophthalmic sign in some patients with Gorlin's syndrome. Recognition of this association may help with earlier diagnosis of Gorlin's syndrome.

References