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ABNORMALITIES OF THE CENTRAL VISUAL PATHWAYS IN PRADER–WILLI SYNDROME ASSOCIATED WITH HYPOPIGMENTATION

DONNELL J. CREEL, PH.D., CATHERINE M. BENDEL, M.D., GEORGIA L. WIESNER, M.S., M.D., JONATHAN D. WIRTSCHAFTER, M.D., DIANE C. ARTHUR, M.D., AND RICHARD A. KING, M.D., PH.D.

Abstract Patients with oculocutaneous or ocular albinism have misrouting of optic fibers, with fibers from 20 degrees or more of the temporal retina crossing at the chiasm instead of projecting to the ipsilateral hemisphere. Misrouting can result in strabismus and nystagmus. Because patients with the Prader–Willi syndrome may also have hypopigmentation and strabismus, we wondered whether they too might have misrouting of optic fibers. We therefore studied six patients with Prader–Willi syndrome selected for a history of strabismus, using pattern-onset visually evoked potentials with binocular and monocular stimulation to look for evidence of misrouted retinal-ganglion fibers. Four had hypopigmentation, and three of these four had abnormal evoked potentials indistinguishable from those recorded in human albinos. The two with normal pigmentation had normal responses. These findings indicate that patients with Prader–Willi syndrome who have hypopigmentation have a brain abnormality characterized by misrouting of retinal-ganglion fibers at the optic chiasm — a finding previously reported only in forms of albinism. (N Engl J Med 1986; 314: 1606-9.)

THE Prader–Willi syndrome is a congenital disorder that includes infantile hypotonicity; hyperphagia, with obesity developing after the neonatal period; hypogonadism; mental retardation; short stature; and small hands and feet.[1-5] Specific clinical characteristics of this syndrome are relevant to analyses of the optic systems. Hypopigmentation has recently been recognized as a feature of Prader–Willi syndrome, but with the exception of two case reports, patients with the syndrome who have hypopigmentation are not considered to have albinism.[3,6] Approximately 50 percent of the patients with Prader–Willi syndrome have hypopigmentation. Other features include a high incidence of strabismus (estimates vary from 40 to 90 percent)[1,7] and childhood nystagmus, which has not been sufficiently studied to yield valid estimates of incidence. Anatomical and electrophysiologic studies have shown that mammals with congenital hypopigmentation of the retinal pigment epithelium have chiasmal misrouting of optic fibers, with excess optic fibers from the temporal retina crossing at the optic chiasm instead of projecting to the ipsilateral hemisphere.[8-11] In humans, this abnormality is common in the presence of oculocutaneous and ocular albinism. The misrouting has catastrophic effects on the organization of the lateral geniculate nucleus of the thalamus and the subsequent organization of the visual cortex. The disorganization of the visual cortex can be detected with the scalp-recorded visually evoked potential.[12-18]

We present evidence for visual-tract anomalies in patients with Prader–Willi syndrome who have hypopigmentation. The development of the visual part of the brain in Prader–Willi syndrome appears to be abnormal when hypopigmentation is present.

METHODS

Patients

Six patients with Prader–Willi syndrome who had histories of strabismus were selected for study. Evaluation included a medical and family history, descriptive and comparative information about the pigment status of the patient's nuclear family, a physical examination, and cytogenetic analysis. Not all the patients were obese at the time of this study, because some had been involved in a weight-reduction program. To meet the criteria for hypopigmentation, a patient had to have the lightest skin in the family and translucency of the iris on globe transillumination.[6] Patients' skin was typed for tanning ability with the criteria of Fitzpatrick: Type I, skin always burned and never tanned; Type II, skin usually burned and tanned less than average; Type III, skin sometimes burned mildly and

From the Veterans Administration Medical Center and the Department of Ophthalmology, University of Utah School of Medicine, Salt Lake City; the Departments of Medicine, Pediatrics, Ophthalmology, and Laboratory Medicine and Pathology, and the Institute of Human Genetics, University of Minnesota School of Medicine, Minneapolis. Address reprint requests to Dr. Creel at Research 151A, VA Medical Center, Salt Lake City, UT 84148.

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tanned an average amount; and Type IV, skin rarely burned and tanned with ease.[19] Iris translucency during transillumination of the globe was rated on the following scale: 0, full pigmentation of the iris with no translucency; 1+, minimal iris depigmentation with slight translucency in a focal pattern; 2+, moderate depigmentation of the iris with diffuse or radial translucency; 3+, marked depigmentation of the iris with prominent translucency and no visualization of the lens; and 4+, marked depigmentation of the iris with prominent translucency and visualization of the margin of the lens. The clinical characteristics and results of testing in six patients with Prader–Willi syndrome are described in Table 1.

Visually Evoked Potentials

Optic misrouting associated with hypopigmentation can be detected by comparing visually evoked potentials elicited by binocular and monocular stimulation while recording from the left and right occipital scalp. Hemispheric asymmetry can be detected by visual inspection of the visually evoked potentials and by determining the difference between potentials recorded from the left and right occipital scalp.[16] Statistical analysis is not necessary. The natural asymmetry of visually evoked potentials often found in recordings from the two occipital scalps is not a factor. The important feature is the difference between the visually evoked potentials when binocular stimulation is compared with individual stimulation in each eye. In subjects with normal pigmentation, there is little difference in the potentials between monocular and binocular stimulation when one is recording from a horizontal array of electrodes overlying the occipital scalp. In subjects with ocular hypopigmentation, such as albinos, the visually evoked potentials after monocular stimulation are quite different when the hemispheres are compared. Most often, monocular stimulation produces a change in the polarity of the components appearing between 75 and 125 msec. This finding is demonstrated by recording the bipolar potential between the occipital poles — e.g., 01 to 02. There will be no change in this "difference potential" when monocular stimulation is shifted from one eye to another in a normally pigmented person (Fig. 1). In an albino, however, there will usually be a dramatic shift in the polarity of the difference potential recorded from each occipital pole when monocular stimulation of the left and right eyes are compared, because nearly all retinal-ganglion fibers originating in the central 20° cross at the optic chiasm. The most efficient stimulus for detecting misrouted optic fibers is pattern onset.[16]

Stimuli were presented on a television monitor 1 m from the subject. The total visual field subtended 20°. The visual stimulus viewed by each patient on the television monitor was a display of 50-minute black-and-white checks of maximal contrast that appeared on the screen for 600 msec and disappeared, to be replaced by a neutral gray for 600 msec. Electrical responses to 100 pattern-onset stimuli were averaged. An artifact-reject program omitted responses contaminated by muscle artifact. Pattern-onset and pattern-offset visually evoked potentials were averaged after binocular and monocular stimulation of each eye. Two sets of averages were recorded in each condition to ensure the reliability of the potentials. Subjects wore their glasses so that they were tested with their best corrected vision.

Patients were seated in a padded, reclining chair in a darkened room. Disk electrodes were attached to the scalp with collodion according to the International 10-20 system. Electrodes located at 01, 02, and OZ were referred to linked ears (A1 + A2), and the bipolar difference potential was recorded between locations 01 and 02. Location CZ was used for grounding. Resistances were equal and less than 5000 ohms. Visually evoked potentials were stored on floppy disks and plotted on x–y graph paper for measurement.

Cytogenetic Methods

Elongated late-prophase and early-metaphase chromosomes were obtained from peripheral-blood lymphocytes with use of a modification of the methotrexate cell-synchronization technique.[20] Ten G-banded spreads were analyzed, and the number 15 chromosomes were examined in additional spreads as needed. Karyotypes were designated according to the International System for Human Cytogenetic Nomenclature, 1985.[21]

Results

Responses to pattern-onset stimuli were normal in the two patients with normal pigmentation (Patients 5 and 6) and in one of the patients with hypopigmentation (Patient 4). As in the responses shown in Figure 1, there was no significant change when binocular and monocular pattern-onset visually evoked potentials were compared. However, the other three patients with hypopigmentation (Patients 1 through 3) had abnormalities in their pattern-onset visually evoked potentials when binocular and monocular stimulation were compared. The responses of Patient 1 are shown in Figure 2. The dramatic reversal in polarity of the principal component appearing between 75 and 100 msec when left and right monocular stimulation are compared — best seen in the difference potential (Fig. 2, line 1) — is evidence of probable substantial misrouting of retinofugal ganglion fibers.

The G-banded karyotypes of the subjects are listed in Table 1. Five of the six subjects had a small interstitial deletion of the proximal long arm of one chromosome 15 in all the cells examined.

Discussion

The Prader–Willi syndrome is a complex multisystem disease of unknown origin. The characteristic features of mental retardation, abnormal appetite control, and abnormal endocrine function could be evidence of a primary abnormality of the brain, but

Table 1. Clinical Characteristics and Results of Cytogenetic Analysis in Six Patients with Prader–Willi Syndrome.*

Patient	Sex/Age	Weight	Height	Banded Karyotype	Hair Color	Skin Type†	Hypopigmentation	Iris Translucency‡	Strabismus	Nystagmus	VEP Abnormal
		percentile									
1	F/31	>95	<3	46,XX,del(15)(q11.2q13)	Red	I	+	3+	+	Childhood	+
2	M/22	>75	10	46,XY,del(15)(q11.2q13)	Blond	II	+	3+	+	–	+
3	F/25	>80	<3	46,XX,del(15)(q11.2q13)	Blond	II	+	2+	+	Childhood	+
4	F/28	>92	<3	46,XX,del(15)(q11.2q13)	Blond	II	+	1+	+	–	–
5	M/21	>85	<3	46,XY,del(15)(q11.2q13)	Brown	III	–	1+	+	–	–
6	F/22	15	<5	46,XX	Brown	II	–	0	+	–	–

*VEP denotes visually evoked potential.

†According to the criteria of Fitzpatrick (see text).

‡See text.

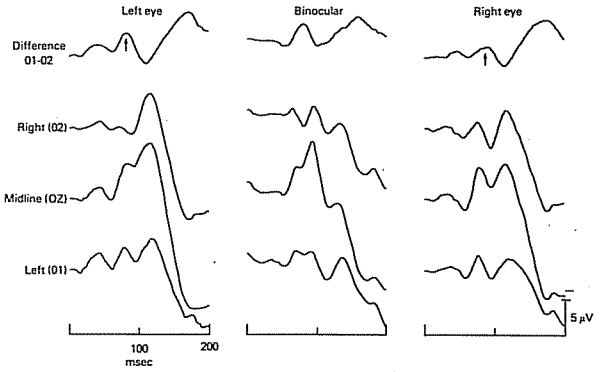

Figure 1. Binocular and Monocular Visually Evoked Potentials Following Pattern-Onset Stimulation in a Person with Normal Pigmentation.

The difference potential (01-02) indicates no significant change in the polarity of the principal component appearing between 75 and 100 msec. The negative direction is up.

no consistent structural abnormalities have been documented.[1,22,23] Abnormalities of the hypothalamus could explain many of these features, but at autopsy the hypothalamus has been found to be structurally normal.[1,23]

Brain structure can be evaluated indirectly by electrophysiologic methods. Abnormalities of the decussation of the optic tract at the optic chiasm, producing subsequent anomalies in the lateral geniculate nucleus of the thalamus and visual cortex, have been documented with studies of visually evoked potentials in patients with severe congenital hypopigmentation resulting from ocular albinism.[12-18] The recent recognition that hypopigmentation occurs with strabismus in about half the patients with Prader–Willi syndrome suggested that abnormalities of the visual system similar to those found in severe forms of congenital hypopigmentation may be present in these patients.

We selected six patients with Prader–Willi syndrome who had a history of strabismus. Four were classified as having hypopigmentation on the basis of specific criteria that included skin and eye pigmentation and a comparison of skin pigmentation with that of other family members, but none of the subjects had severe hair or skin hypopigmentation consistent with the diagnosis of albinism.[6] Translucency of the iris during globe transillumination was another criterion for hypopigmentation in Prader–Willi syndrome; it was most marked in the three subjects with optic-tract misrouting.

We found other ophthalmologic features similar to those of albinism. Oculocutaneous and ocular forms of albinism are characterized by translucency of the iris, strabismus, and nystagmus. All six of the patients we selected had a history of strabismus. According to the literature, the percentage of patients with Prader–Willi syndrome who have strabismus ranges from 40 to 90 percent.[1,7]

Acquired strabismus frequently results from unequal visual stimuli from each eye into the brain. There are several reasons why albinos or patients with optic misrouting would be vulnerable to strabismus. Misrouting of the neurons originating in the temporal retina disturbs the orderly representation of visual space in the brain.[8,16] The consequence of this is that cortical cells do not receive normal binocular stimulation, and this results in an abnormality of the anatomical substrate underlying binocular vision. Optic misrouting also exaggerates the nasotemporal difference in the organization of the visual system.[24] These differences include the function and ontogeny of the nasal and temporal portions of the retina — e.g., fibers originating in the nasal retina predominate over fibers of temporal origin in number and in the time of their appearance.[12,13] Misrouted optic fibers also terminate in the superior colliculus and pretectal areas, resulting in essentially complete decussation of the phylogenetically older projections to those areas that control eye movement. Each of these factors produces disparate visual information, which goes to both cortical and midbrain visual centers.[12] Increased light scattering in the eye of an infant with hypopigmentation and poor visual feedback due to nystagmus may aggravate strabismus.[24]

Two of the three patients we studied who had evidence of optic misrouting also had a history of childhood nystagmus. Nystagmus can be a key indicator of optic-tract misrouting, because fixation nystagmus is often symptomatic of poor foveal development. The two patients with Prader–Willi syndrome and a history of childhood nystagmus appeared to have a poorly formed fovea. The fundus in Patient 1 was very pale, the macular region was less pigmented than usual, and the foveal region was not well developed. In Patient 3 the macular region was recognizable but hy-

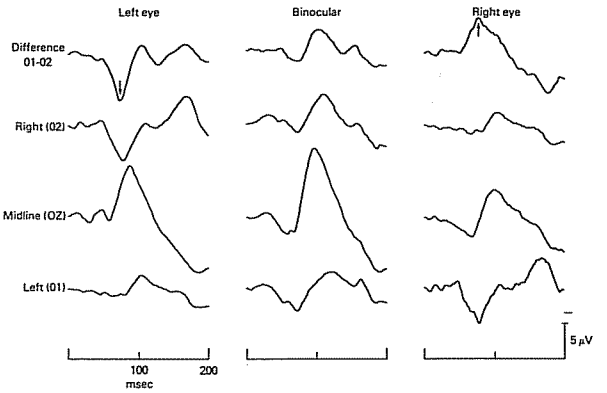

Figure 2. Binocular and Monocular Visually Evoked Potentials Following Pattern-Onset Stimulation in a Patient with Prader–Willi Syndrome Who Had Hypopigmentation and a History of Nystagmus and Strabismus (Patient 1).

The difference potential (01-02) indicates a marked change in the polarity of the principal component appearing between 75 and 100 msec. The negative direction is up.

popigmented. The fovea was also recognizable but did not appear normal. In all the other patients the macular regions were well defined and the fovea recognizable.

The changes in the pattern-onset visually evoked potential between binocular and monocular stimulation in Patients 1 through 3 with Prader–Willi syndrome were indistinguishable from the potential that has been recorded in persons with ocular and oculocutaneous albinism.[16] The visually evoked potential of the two patients with Prader–Willi syndrome who had normal pigmentation were normal. We have no explanation for the absence of the abnormal potential in one patient with hypopigmentation; it was probably a result of an imprecise definition of hypopigmentation. Quantitative biochemical methods will be required to define specifically the presence or absence of a minimal-to-moderate reduction in pigment synthesis.

No correlation was found between the presence of hypopigmentation, an abnormal visually evoked potential, and a deletion of the long arm of chromosome 15. All patients with hypopigmentation had the deletion, but this was also true of one patient with normal pigmentation. Three patients with the deletion had an abnormal visually evoked potential, and two did not.

The cause of misrouted optic projections and the associated structural changes in the brain and visual cortex in hypopigmented mammals is unknown. The principal correlate of normal optic projections is the presence of melanin pigment in the retinal pigment epithelium. The melanin itself, or a chemical mediation related to the presence of melanin pigment, is a likely prerequisite for normal development of the optic system during embryogenesis.[25,26] There is also support for the position that misrouting is due to a timing error in ontogeny.[12,13,27]

Hypopigmentation has only recently been recognized as an important feature of the Prader–Willi syndrome phenotype.[3,6] This study emphasizes the fact that about half the patients with Prader–Willi syndrome may have optic-tract misrouting and associated brain abnormalities. Because we specifically selected patients who had strabismus or nystagmus, our small series may overrepresent the true incidence of optic-tract misrouting in Prader–Willi syndrome. Investigations in larger numbers of unselected patients and morphologic studies will be needed to document the exact incidence.

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