VISUAL AND AUDITORY ANOMALIES IN CHEDIAK-HIGASHI SYNDROME

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The Chediak-Higashi syndrome (CHS) is a rare form of partial albinism which was initially recognized as a disorder of leukocyte morphology in which neutrophils, monocytes and lymphocytes contained giant cytoplasmic granules (Chediak 1952; Higashi 1954). The syndrome is further characterized by increased susceptibility to infection (Blume and Wolff 1972; Boxer and Stossel 1982) along with prolonged bleeding times resulting from impaired platelet function (Buchanan and Handin 1976; Boxer et al. 1977). Apparent hypopigmentation is the result of the aggregation of abnormally large melanosomes (Witkop et al. 1978). Their hair is an unusual metallic, frosted gray color. Ocular anomalies include pale irises, albinotic fundi, moderate photophobia and forms of nystagmus and strabismus. If they survive the recurrent infections of childhood, a progressive neuropathy frequently develops manifested by cranial and peripheral polyneuropathy, muscle weakness, foot drop, decreased muscle stretch reflexes and often ataxia (Kritzler et al., 1964; Lockman et al. 1967).

Since CHS is considered a form of oculocutaneous albinism it is reasonable to assume that CHS may include auditory and visual anomalies that appear in conjunction with ocular and oc-
Subjects

Four patients with CHS were tested. Two were brothers aged 30 and 31 and two were unrelated 6-year-old girls (Boxer et al. 1979). All four fulfilled the criteria for CHS (Blume and Wolff 1972). Both males exhibited peripheral neuropathy with limb hypotonia and one had bilateral foot drop requiring bracing. One male had severe hypotonia of the esophagus with esophago-gastric reflux requiring surgery. It is suspected that he also has gastrointestinal neuropathy of the lower gut similar to the diabetic type since he has frequent diarrhea and poor sphincter tone and control. The EEG of both adult males demonstrated diffuse slowing of background activity. There were, however, no focal or epileptiform abnormalities or evidence of lateralized pathology. There were no apparent neurological deficits in the two girls except for ophthalmological symptoms. One girl demonstrated a mild strabismus and the other moderate nystagmus. Both males and the girl with nystagmus failed the Titmus stereovision test indicating lack of binocular stereovision. The girl with strabismus performed normally when tested for stereovision.

Methods

Optic misrouting associated with hypopigmentation can be detected by comparing VEPs elicited by binocular and monocular stimulation while recording from left and right occipital scalp. Evidence of optic misrouting can be detected by visual examination of the VEPs. Statistical analysis is not necessary.

The most efficient stimulus for detecting misrouted optic fibers is pattern onset (Creel et al. 1981). Stimuli were presented on a TV monitor 1 m from the subject. The TV screen subtended 20° of visual field. A computer controlled display of 50' checks of maximum contrast that appeared for 500 msec and disappeared to a neutral gray of equal total luminance for 500 msec. One hundred responses to pattern onset were averaged for binocular and monocular conditions. The bandwidth of the EEG amplifiers was 1–100 Hz (±3 dB).

By analogy with the model of the visual system, significant alteration in decussation of auditory pathways should be reflected in the comparison of the ABRs recorded from each hemisphere after monaural stimulation. It has been reported that an ABR recorded from the electrode configuration of vertex referred to the ear ipsilateral to monaural stimulation (Cz-Ai), compared to the ABR recorded between the vertex and the ear contralateral to stimulation (Cz-Ac) correctly lateralizes pathology in the brain stem (Oh et al. 1981). rarefaction clicks of 100 μsec duration and an intensity of 70 dB HL were presented monaurally through TDH-39 earphones at a rate of 11.3/sec. Potentials evoked by 2000 clicks were averaged; the period of analysis was 10 msec from the onset of each click. The bandpass setting was 150–3000 Hz (±3 dB).

The participants had normal hearing. Subjects were seated in a padded chair in a darkened, sound-deadened and electrically shielded room. Disc electrodes were attached according to the 10-20 system. For recording VEPs scalp electrode locations O1 and O2 were referred to linked ears (A1 + A2), with Cz being used for ground. ABRs were recorded from Cz referred to the ipsilateral ear (Ai) and contralateral ear (Ac). Resistances were equal and below 3000 Ω.

Results

The VEPs evoked by onset stimuli were normal in form and hemispheric symmetry following binocular stimulation. However, all 3 CHS individuals that failed the stereovision test demonstrated abnormal VEPs following monocular stimulation. Monocular stimulation of either eye produced a significant attenuation of components in the first 125 msec of the VEP recorded from the hemisphere ipsilateral to the stimulated eye (Fig. 1).
The ipsilateral ABRs (Cz-A₁) of all 4 CHS subjects were normal in form and peak latencies. The amplitude of components of ABRs recorded from all 4 CHS subjects was approximately one-half the amplitude of components of normally pigmented subjects. Also, contralateral ABR (Cz-A₉) positive components peaking between 3 and 5 msec were significantly attenuated or completely reversed in polarity and prolonged in latency (Fig. 2).

Discussion

In hypopigmented individuals, such as oculocutaneous or ocular albinos, the VEPs following monocular stimulation are quite different when hemispheres are compared. Monocular stimulation most often produces a change of polarity or attenuation of early VEP components recorded from the occipit ipsilateral to the eye stimulated (Taylor 1978; Coleman et al. 1979; Creel et al. 1981). Monocular VEPs of the 3 CHS subjects that failed
the stereovision test resembled abnormal VEPs of traditional forms of oculocutaneous albinism. The hemispheric asymmetry of monocular VEPs of these CHS subjects, along with the anatomical evidence from studies of mink (Sanderson et al. 1974; Guillery et al. 1979), mice (LaVail et al. 1978) and cats (Creeel et al. 1982) with CHS provide substantial evidence that most humans with CHS probably have misrouted retino-geniculo-striate projections. The failure to perform the stereovision test is further confirmation that misrouting of optic neurons has disturbed the anatomical substrate underlying binocular vision at the cortical level. The observation that one subject with CHS had normal monocular VEPs and also performed normally on the stereovision test indicates probable variable expression of visual anomalies in humans with CHS.

Previous studies of ABRs recorded from electrodes ipsilateral (Cz-A1) and contralateral (Cz-A2) to monaural stimulation in human albinos indicate an asymmetry of ABRs with positive components peaking between 3 and 5 msec in the contralateral ABR being significantly attenuated in amplitude (Creeel et al. 1980). Similar differences have been reported for albino cats (Creeel et al. 1983). The complex spatial and temporal relationship of neuronal generators of early components of ABRs precludes any simple 1:1 relationship between a given anatomical site and a particular component of the ABR. However, there is general agreement concerning the principal generators of components that appear in the first 5 msec (e.g., Stockard and Rossiter 1977; Achor and Starr 1980a, b; Buchwald et al. 1981; Hashimoto et al. 1981). In all studies of both albino humans and cats the components that are attenuated in amplitude or missing from the contralateral ABR are those components most often associated with neuronal sites at the level of the initial decussation of auditory fibers, i.e., the superior olivary nuclei and trapezoid body. Results from studies of ABRs of both albino humans (Creeel et al. 1980) and cats (Creeel et al. 1983) and the present data from humans with CHS suggest anomalies in brain stem auditory structures involved in transmitting information to the contralateral hemisphere, most likely via the acoustic striae, trapezoid body and superior olivary nuclei.

It is unlikely that anomalies in the central auditory system are truly analogous to misrouting in the visual system. More likely, the paucity of pigment in the inner ear may be related to a neuronal cascade of changes which affects the cochlear nuclei and acoustic striae. The smaller amplitude ABR recorded from albino cats and the subjects with CHS in this study may be due to fewer or smaller diameter axons in their peripheral and/or central auditory system. Since the older individuals with CHS manifest polyneuropathies, these multiple neural degenerations may contribute to their sensory anomalies.

Until this study the Chediak-Higashi syndrome was not known to include central sensory deficits. However, CHS is generally classified as a form of oculocutaneous albinism and visual anomalies have been described in the traditional forms of oculocutaneous albinism (see Taylor 1978; Witkop et al. 1978 for reviews). Anomalies of the central auditory system also appear to exist in oculocutaneous albinism (e.g., Henry and Haythorn 1975; Maxson 1979; Creeel et al. 1980, 1983). Although the hair, skin and irises are relatively well pigmented in CHS, these individuals apparently have anomalies of their central visual and auditory pathways.

Summary

Albinism is correlated with misrouting of decussating retinal fibers in the brain. There is also evidence of anomalies of decussating auditory pathways in albinos. The Chediak-Higashi syndrome (CHS) is a rare form of partial albinism which includes increased susceptibility to infections, a hemorrhagic tendency and peripheral polyneuropathies. Binocular and monocular pattern-onset visually evoked potentials (VEPs) and monaural auditory brain stem responses (ABRs) were recorded from 4 subjects with CHS. Three of the CHS demonstrated asymmetric monocular VEPs and failed the Titmus stereovision test. All 4 CHS produced asymmetric ABRs similar to those reported for albinos. Although the hair, skin and irises are relatively well pigmented in CHS, these individuals apparently have anomalies of their central visual and auditory pathways.
Résumé

Anomalies visuelles et auditives dans le syndrome de Chediak-Higashi

L'albinisme s'accompagne d'une perturbation de la décussation des fibres rétiniennes dans le cerveau. Il existe également des données concernant des anomalies de décussation des voies auditives chez l'albinos. Le syndrome de Chediak-Higashi (SCH) est une forme rare d'albinisme partiel qui s'accompagne d'une augmentation de la sensibilité aux infections, d'une tendance aux hémorragies et de polynéuropathies périphériques. Les potentiels évoqués visuels à l'apparition d'un pattern présenté soit en monoculaire, soit en binoculaire, ainsi que les réponses auditives monaurales du tronc cérébral ont été enregistrés chez 4 sujets SCH. Trois des 4 patients ont présenté des PEV monoculaires asymétriques et n'ont pas réussi le test Titmus de Stéréovision. Les 4 sujets SCH ont développé des réponses auditives du tronc cérébral asymétriques identiques à celles déjà rapportées pour les albinos. Bien que les cheveux, la peau et l'iris soient relativement bien pigmentés chez les SCH, ces sujets présentent apparemment des anomalies dans les trajeots suivis par les voies centrales visuelles et auditives.

References


