

Vestibular dysfunction in familial dysautonomia

The Riley-Day syndrome

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Siggers, D. C., Haciska, D. T., and McKusick, V. A. (1975). *Archives of Disease in Childhood*, 50, 890. **Vestibular dysfunction in familial dysautonomia: the Riley-Day syndrome.** We report the bilateral absence of response to tests of vestibular function in 5 patients with familial dysautonomia.

Familial dysautonomia (Riley *et al.*, 1949) is an autosomal recessive disease affecting Jews of Eastern European ancestry (Brunt and McKusick, 1970). As the name implies the autonomic nervous system is defective, and this is seen clinically as defective control of temperature, blood pressure, and swallowing, by skin blotching, excessive sweating, lack of tearing, and bowel disturbance. Abnormalities are also present in the sensory nervous system, and these include diminished ability to taste, relative insensitivity to pain, and dysaesthesia. The absence of deep tendon reflexes may also be the result of a sensory deficit in the afferent side of the reflex arc. Joint position sense is, however, normal and no satisfactory explanation has to our knowledge been given for the frequent findings of balance disturbance and a positive Romberg sign in dysautonomia. We report the finding of abnormal vestibular function in this disorder.

Patients and methods

Five patients were studied; these were an unselected group, being the first 5 patients ascertained from the region. All were of Jewish ancestry and each was a classical case of familial dysautonomia. 4 were male and 1 was female, ranging in age from 8 to 17 years. All had normal hearing and all had otoscopically normal ear canals and tympanic membranes. The vestibular examination was performed with electronystagmographic recording of eye movements recording the potential differences between the cornea and the retina. All the patients were examined for spontaneous and gaze deviation nystagmus, positional nystagmus, and induced eye movements; namely optokinetic and

vestibular nystagmus. The caloric stimulation was performed with the patient in the supine position with the head flexed 30 degrees from the horizontal plane so as to bring the horizontal semicircular canals into a vertical plane. Irrigation was performed for 40 seconds with water at temperatures 7 °C above and 7 °C below body temperature, alternating between the two external auditory canals (Fitzgerald and Hallpike, 1942). A period of 5 minutes was allowed between irrigations. Finally stimulation was performed with 20 ml of water at 0 °C on each canal. For evaluation of the responses the maximum velocity of the nystagmus between the 60th and 90th seconds after onset of irrigation was determined (Stahle, 1958).

Results

A summary of the responses of the 5 patients to the above tests is shown in the Table. Normal individuals do not show spontaneous nystagmus, gaze deviation nystagmus, or positional nystagmus but develop nystagmus in response to the alternate hot (44 °C) and cold (30 °C) caloric test. 20 cm³ of water at 0 °C is considered a maximum stimulus and is used only to seek a response in individuals who do not respond to the alternate hot (44 °C) and cold (30 °C) caloric test. Optokinetic nystagmus is always present in normal individuals. All 5 patients showed bilateral absence of response to alternate hot (44 °C) and cold (30 °C) caloric tests and to 0 °C (20 ml) caloric stimulation with the exception of Case 4 who showed some beats of low intensity nystagmus bilaterally to the 0 °C caloric test, and one other, Case 1, who showed low intensity nystagmus on the right to the 0 °C caloric stimulation. All 5 had normal optokinetic nystagmus. One had bilateral symmetrical gaze deviation nystagmus. Fig. 1 shows a typical

TABLE

Summary of the responses of dysautonomic patients and normal controls to tests of vestibular function

Case no.	Age (yr)	Gaze deviation nystagmus		Spontaneous nystagmus	Positional nystagmus	Horizontal optokinetic nystagmus	Caloric tests	
		R	L				Hallpike's caloric test	20 ml at 0°C
1	10	—	—	—	—	+	—	±*
2	13	—	—	—	—	+	—	—
3	17	—	—	—	—	+	—	—
4	8	—	—	—	—	+	—	++
5	16	+	+	—	—	+	—	++†
Normal controls		—	—	—	—	+	++	+++

*Low intensity nystagmus on right.
 †Low intensity nystagmus bilaterally.
 +, response; —, no response.

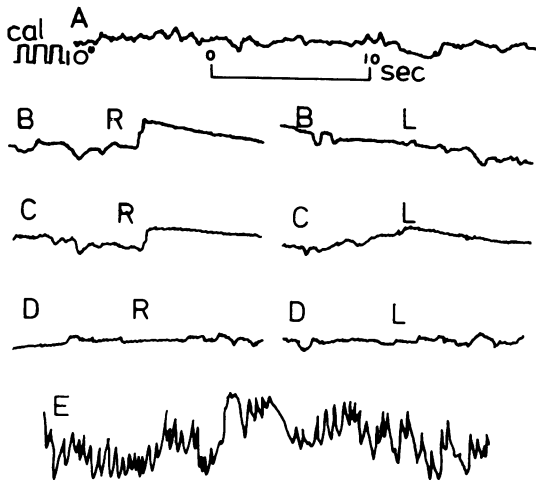


FIG. 1.—A recording from a 17-year-old female with familial dysautonomia (Case 3) showing bilateral total loss of vestibular function and normal optokinetic nystagmus. (A) Recording, in the supine position, in which no spontaneous nystagmus is present. (B), (C), (D) The recordings of the caloric reaction at 44 °C, 30 °C, and 20 ml at 0 °C, respectively (60–90 s after starting syringing) showing a lack of caloric response. Right canal and left canal, respectively. (E) Optokinetic nystagmus normal.

caloric response from a dysautonomic patient compared with a normal caloric response shown in Fig. 2. A recording from a patient (Case 4) with low intensity nystagmus induced only by caloric stimulation using 20 ml of 0 °C water is shown in Fig. 3.

Discussion

We have been interested in the possible role of

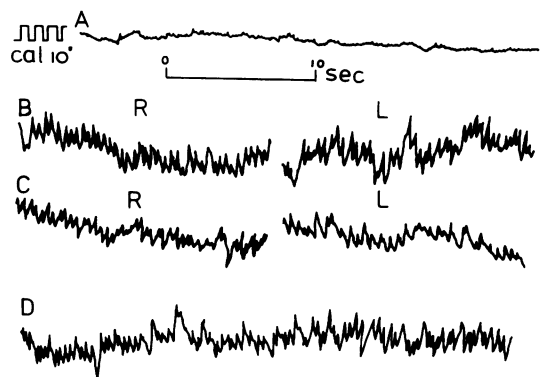


FIG. 2.—A recording from a normal subject showing normal bithermal caloric reaction and optokinetic nystagmus. (A) recording in the supine position, in which no spontaneous nystagmus is present. (B), (C). Recordings of the caloric response at 44 °C and 30 °C (60–90 s after starting syringing). Right canal and left canal, respectively. (D) Optokinetic nystagmus.

nerve growth factor (Levi-Montalcini and Angeletti, 1968) deficiency, or the lack of response of target tissues to nerve growth factor, in the pathogenesis of familial dysautonomia (Dancis and Smith 1966; Aguayo, Martin, and Bray, 1972). Hillman and Sheikh (1968) reported that nerve growth factor promoted the outgrowth of axons from vestibular neurons in the rabbit. This information, and the clinical findings of a disturbance in balance, positive Romberg sign, and normal proprioception in dysautonomia, suggested to us the possibility of vestibular dysfunction in this disorder.

The vestibulo-ocular reflex arc functions to stabilize the visual axes in space and to maintain the retinal image in the same position. The vestibular

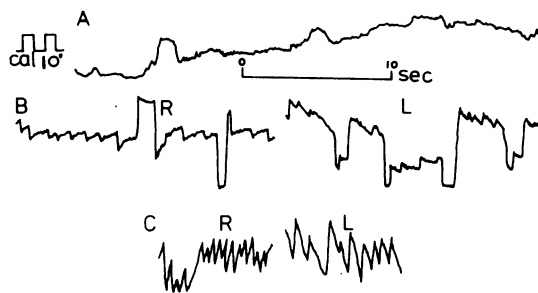


FIG. 3.—An 8-year-old male (Case 4) with familial dysautonomia showing diminished sensitivity of both sides. (A) Recording in the supine-position, showing no spontaneous nystagmus. (B) The caloric test with 20 ml of 0 °C water shows obviously diminished sensitivity of both sides, right and left respectively. (C) Optokinetic nystagmus normal.

impulses, which are initiated by the deflection of the cupula, travel by two principal pathways to the extraocular muscles. The first and shorter pathway is the three-neuron arc, consisting of the primary vestibular neuron, the secondary neuron ascending from the vestibular nuclei via the middle longitudinal fasciculus to the oculomotor nuclei, and the motor neurons innervating the extrinsic eye muscles (Ladpli and Brodal, 1968; Gernandt, 1968). The second pathway consists of longer internuncial chains and includes the multisynaptic connexions of the reticular formation (Ladpli and Brodal, 1968; Brodal, Pompeiano, and Walberg, 1962; Lorenete de N6, 1933, 1938; Szentágothai, 1950). Lesions in the above structures could produce either disturbance or absence of the responses conducted by the vestibulo-ocular reflex arc.

Our study showed bilateral lack of induced vestibular responses to the Hallpike caloric test in all 5 patients examined. Such bilateral canal paresis is usually seen only in peripheral vestibular disorders with the pathology localized either in the labyrinth (for example, labyrinthitis, transverse temporal bone fractures, or drug toxicity such as from streptomycin) or in the first vestibular neuron (for example, in vestibular neuronitis, meningitis, or cerebellopontine angle tumours). A lesion within the labyrinth itself is very unlikely in our subjects in view of their normal hearing and also because histopathological examination of the vestibular organ in familial dysautonomia (Kelemen, 1968) has shown an essentially intact vestibular end organ, including cupulae of the cristae and utricular maculae.

If most vestibular impulses are conducted through

the reticular formation to the oculomotor nuclei (Scheibel and Scheibel, 1958) the lesion in dysautonomia could be central, namely demyelination in the reticular formation which is a finding common to two necropsy reports in familial dysautonomia (Brown, Beauchemin, and Linde, 1964; Cohen and Solomon, 1955). If the lesion was in the reticular formation one would not expect the complete absence of induced vestibular responses but possibly a distortion of the nystagmic pattern with loss of the quick component, which was not found in these cases. The finding of diminished numbers of neurons in the dorsal root ganglia (Pearson, Budzilovich, and Finegold, 1971) and of axons in peripheral nerves (Aguayo, Nair, and Bray, 1971) in dysautonomia suggests to us the possibility that the lesion might be peripheral, namely a reduction in the neurons of the vestibular ganglion which in consequence would produce marked reduction of the induced vestibular responses with no involvement of hearing. The precise localization of the lesion will, however, have to await detailed histological study of the primary vestibular neuron, the vestibular nuclei, and the secondary vestibular pathways

Bilateral lack of peripheral vestibular function can usually be compensated in man to a great extent by optical or proprioceptive mechanism. Patients with a dysfunction such as we describe here are usually able to walk satisfactorily in the light, but in the dark they stagger and fall. They are not able to maintain ocular fixation when the head is moving, because of inability to correlate eye movement. Riding a bicycle is often impossible or very difficult for these patients. Body position sense is impaired and there is absence of the sensations of acceleration and deceleration. Such a lack of body position sense can be hazardous when swimming because beneath the surface the only means left of finding the upward direction is visual. If visual localization of the surface is impaired for any reason, directional orientation is lost. One wonders indeed whether the cases of drowning reported in this disorder may have occurred at least in part on this basis in addition to the hypoxia which has been previously suggested (Filler *et al.*, 1965). Parents should be warned that dysautonomic children should not be allowed to dive because they may swim away from, rather than towards, the surface. Vestibular dysfunction in dysautonomia may be the cause or partial cause of the delay in physical milestones, such as sitting and walking; and possibly of the episodes of uncontrollable vomiting.

These findings resulted from the consideration of a nerve growth factor defect in the pathogenesis

of dysautonomia. Perhaps this hypothesis will prove correct, and deficient or defective nerve growth factor may be found in the future to play a part in other human disorders.

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