Ocular responses to autonomic drugs in familial dysautonomia

Alfred A. Smith, Joseph Dancis, and Goodwin Breinin

Familial dysautonomia presents a tetrad of symptoms referable to the eye which are quite regularly present and which, in association, are distinctive and virtually diagnostic. These are alacrima, corneal hypesthesia or anesthesia, exodeviation, and pupillary constriction following the local administration of 2.5 per cent methacholine. These manifestations appear to be related to other symptoms of the disease.

Familial dysautonomia is a rare, inherited disease affecting the motor, autonomic, and sensory nervous systems. The patients suffer from postural hypotension, emotional lability with hypertensive and vomiting episodes, excessive sweating, and blotching of the skin. The presenting symptoms may involve the eyes—alacrima, corneal anesthesia, and trophic lesions of the cornea.

In the present study, dysautonomic children have been examined in order to define better the ophthalmologic disorder and possibly gain further insight into the mechanisms of the disease. In the course of the study, an abnormal response to methacholine has been recognized which may serve as a diagnostic test.

Materials and methods

Methacholine hydrochloride (Mecholyl) was freshly prepared as a 2.5 per cent solution in distilled water just prior to use. The epinephrine solution (USP) contained a small quantity of norepinephrine. Cocaine hydrochloride and neostigmine were employed as 5 per cent solutions. Phospholine iodide was provided by Campbell Pharmaceuticals.

The subjects with dysautonomia ranged in ages between 6 and 24 and presented the clinical characteristics of the disease. In addition, they had an abnormal response to intradermal histamine and demonstrated deficient taste discrimination.

For the response to local administration of pharmacologic agents, one drop of the test solution was placed in the conjunctival sac and held for 10 seconds. The pupils were then examined periodically over the next 30 minutes. Pupillary sizes were examined initially by means of a transparent ruler and at constant illumination. The diameter of the pupils ranged from 4 to 5 mm.

The response to methacholine was usually marked (greater than 2 mm. change) so that the majority of the studies were subsequently done by simple comparison with the control eye. The corneas of 2 of the children who had a marked miotic response to methacholine were examined by means of a slit lamp and fluorescein stain, but no abnormalities were detected. None of the dysautonomic subjects tested with drugs showed gross evidence of corneal abnormality. The response to methacholine was also tested in 14 persons having a variety of corneal lesions, and in 5 children tested immediately after tonometry.

Methacholine was administered systemically to 6 control and 6 dysautonomic subjects by in-
travenous infusion at controlled rates in solutions of 25 to 100 μg per milliliter of isotonic saline. An increase in the flow of tears was determined by inspection. Ocular deviation was evaluated by Miss H. Dendy, orthoptist in the Department of Ophthalmology.

Results

The instillation of 0.1 per cent 1-epinephrine ordinarily produces no pupillary change. Cocaine, however, does produce mydriasis in normal individuals. These findings indicate an intact sympathetic innervation to the dilator muscles of the iris. As shown in Table I, patients with dysautonomia give the normal responses.

In contrast with the normal,16 of 18 patients with dysautonomia developed miosis within 30 minutes following instillation of methacholine, 2.5 per cent. The miosis was marked in 14 (more than 2 mm. change in diameter) and moderate but easily seen in 2 others when compared with their untreated eye. The remaining 2 patients failed to respond even after repeated instillations of methacholine. These last subjects also showed a much milder form of the disease than the others.

The cholinesterase inhibitors, neostigmine and phospholine, constricted the pupils in each of the 7 dysautonomic subjects tested. The miosis induced by phospholine persisted for many hours.

To determine whether the presence of inapparent corneal lesions in the dysautonomic enhanced the penetration of methacholine into the anterior chamber, a group of 14 adults with a variety of corneal lesions and a group of 5 children just examined with a tonometer were tested with methacholine, 2.5 per cent. In these individuals existing corneal lesions and tonometry did not induce a miotic response to this solution.

When methacholine is infused into normal individuals, tearing usually occurs. In our study (Table II), tearing began at infusion rates of 2.5 to 11.7 μg per kilogram per minute, with a mean of 6.0. The dysautonomic response contrasted sharply; the onset of tearing appeared at rates as low as 0.4 and with a mean of 1.4 μg per kilogram per minute. Overflow tearing was commonly observed only in the dysautonomic subjects.

The difference from normal in the dose of methacholine required to initiate tearing, and the fact that tearing ordinarily does not occur in dysautonomia, suggests denervation supersensitivity of the lacrimal gland.

A further ocular disorder which appears to be part of the dysautonomic syndrome is exodeviation. As shown in Table III, of 15 patients examined by the orthoptist, 12 showed some form of this disorder.

Discussion

A disease with widespread effects on the motor, sensory, and autonomic nervous system.

Table I. Pupillary responses to instillation of drugs into one eye of patients with familial dysautonomia

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of patients</th>
<th>Miosis</th>
<th>Mydriasis</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine, 0.1%</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine, 2%</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methacholine, 2.5%</td>
<td>18</td>
<td>16</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Neostigmine, 5%</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phospholine, 0.125%</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The untreated eye served as a control for pupillary size.

Table II. Infusion rates of methacholine required to initiate tearing in dysautonomic and control subjects

<table>
<thead>
<tr>
<th>Normal Subjects</th>
<th>Dysautonomic Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject</td>
<td>Age/ Sex</td>
</tr>
<tr>
<td>R. D.</td>
<td>22/M</td>
</tr>
<tr>
<td>F. P.</td>
<td>28/F</td>
</tr>
<tr>
<td>M. P.</td>
<td>25/F</td>
</tr>
<tr>
<td>M. C.</td>
<td>13/F</td>
</tr>
<tr>
<td>L. J.</td>
<td>12/M</td>
</tr>
<tr>
<td>J. M.</td>
<td>23/M</td>
</tr>
<tr>
<td>Mean</td>
<td>6.0</td>
</tr>
</tbody>
</table>

*Lacrimation was not evident at the highest infusion rates employed. The normal subjects are listed as responders at these rates for convenience of presentation.
systems is likely to have manifestations in the eye. In fact, the tetrad of ophthalmologic findings—alacrima, corneal hypesthesia or anesthesia, exodeviation, and pupillary constriction following methacholine, 2.5 per cent—is so distinctive as to suggest strongly the diagnosis of familial dysautonomia. The diagnosis can be readily confirmed by the intradermal histamine test and by the absence of fungiform and vallate papillae on the tongue.

Previous studies have demonstrated an exaggerated response in dysautonomia to intravenous infusions of norepinephrine and of methacholine. It was suggested that the exaggerated response to norepinephrine may be the result of deficient synthesis or release of norepinephrine, this suggestion being supported by the finding of reduced urinary vanillyl-mandelic acid. However, it was also pointed out that a deficiency in parasympathetic compensatory response to norepinephrine could also explain the results. Such a parasympathetic deficiency would also account for the supersensitive pupillary responses to methacholine, 2.5 per cent, and for the alacrima correctable by methacholine, first reported by Kroop.

In fact, the lacrimal gland appears to share the supersensitivity to methacholine. The present investigation of the pupillary reactivity to pharmacologic agents has provided further information. Sympathetic denervation results in supersensitivity of the iris muscle to adrenergic agents, whereas parasympathetic denervation induces supersensitivity to cholinergic agonists. Dilute epinephrine produced no response in the dysautonomic subjects, but cocaine, 2 per cent, which produces a sympathetic stimulation by potentiating intrinsic norepinephrine, induced miosis. These results are consistent with an intact sympathetic innervation to the eye.

In 16 of 18 dysautonomic subjects, however, methacholine, 2.5 per cent, produced miosis. Interestingly, the 2 subjects who failed to respond had a mild form of the disease, clinically difficult to diagnose as dysautonomia. The miotic response to dilute methacholine is consistent with a parasympathetic denervation. Whether the postulated denervation is central or postganglionic is unknown, but the miotic responses to neostigmine and phospholine would also account for the supersensitive pupillary responses to methacholine, 2.5 per cent.
strongly suggest that the denervation is incomplete. Both substances are cholinesterase inhibitors and therefore believed merely to augment the effect of endogenous acetylcholine.

There is the possibility that the exaggerated response to methacholine simply reflects increased permeability of the cornea as a result of trophic disturbances. However, patients with definite corneal lesions but without dysautonomia did not respond to dilute methacholine. An abnormal response, moreover, was demonstrable in a dysautonomic infant at the age of 2 weeks before there had been much opportunity for corneal damage to have occurred. In this case a slightly higher concentration of methacholine (3.5 per cent) was used. Normal infants under 6 months of age, however, occasionally respond to dilute methacholine, so that in this age group the diagnosis of dysautonomia requires support by other tests.

The exodeviation parallels the general awkwardness and poor muscular control from which these children suffer. Rombergism, which can also be elicited, suggests a proprioceptive defect. The neurological lesion causing this disturbance is presently unknown, although recent evidence suggests that the widespread sensory deficits in dysautonomia may originate at the receptor sites. The inability to taste dilute sweet or sour solutions has been correlated with a receptor defect—an absence of taste buds. The fungiform papillae and vallate papillae, which contain the taste buds, are absent in the dysautonomic. The respiratory responses to hypoxia and hypercapnea are also subnormal. The axon reflex normally induced by histamine injection is missing in dysautonomia and suggests a peripheral sensory deficit possibly within the cornea. Since these nerve endings can be visualized in the cornea, it may be possible to demonstrate an anatomical basis for pain insensitivity in this organ resembling the absence of taste buds in the tongue.

REFERENCES
13. Dodge, P. R.: Personal communication.