RILEY–DAY SYNDROME*
(CONGENITAL FAMILIAL DYSAUTONOMIA)

BY

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This rare disease is of particular importance to ophthalmologists because of the congenital failure of tear production and corneal anaesthesia. It was first described as an entity by Riley, Day, Greeley, and Langford (1949). Since then, many further cases have been reported (Braun-Vallon and Bessman, 1960; Levin, 1960; Laxdal, Khera, and Haworth, 1961; Thieffry, Joseph, Martin, Job, and Lortholary, 1961). The importance of its recognition by ophthalmic surgeons has been stressed in the American literature (Dunnington, 1954; Liebman, 1956, 1957; Pilger, 1957). No reports have been made of this disease, as such, in the British ophthalmic literature, although Duke-Elder (1930) and Coverdale (1948) included cases which were probably of this disease when considering alacrimia congenita.

The condition occurs in children of Jewish parentage, and is characterized by the following features: failure to thrive, recurrent respiratory infection, diarrhoea, emotional instability, skin-blotching, insensitivity to pain, hyporeflexia, corneal anaesthesia, and failure of lacrimation.

Various other curious features have been reported, namely, spontaneous fractures, as occurred in the case reported here, lability of blood pressure, and abnormal reactions to anaesthesia (Kritchman, Schwartz, and Papper, 1959). Ureteric malformations have been reported by de Toni, Nordio, and Bertolini (1960), and epilepsy by Peralta Serrano (1961).

Case Report

The patient, an 8-year-old girl, was born in May, 1953. She was first seen at the Queen Elizabeth Hospital for Children in February, 1962, where she had been referred for further investigation because of recurrent chest infections, bronchiectasis, lassitude, pyrexia, weight-loss, sweating on eating, fainting, anorexia, and irregular sleep rhythm.

Past History.—Birth-weight, 4 lb. 13 oz. She was born 3 weeks prematurely and her development was slightly retarded in that she did not crawl until the age of 13 months or walk until she was 19 months old.

Previous Illnesses.—She had had two bouts of pneumonia, which were thought to be due to an underlying bronchiectasis. She had also had chicken-pox.

Family History.—The parents were Jewish, unrelated. There was one sibling, and no family history of disease.

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Physical Examination.—She was a thin, tired-looking child, with a pointed chin and shining eyes. She had small hands with clubbed fingers and pes equinovarus.

Respiratory system: evidence of bronchiectasis.

Cardiovascular system: blood pressure 130/80; nothing abnormal discovered.

Central nervous system: fundi normal, cranial nerves normal (corneal reflexes found to be absent later). The only abnormalities detected were absent knee and ankle jerks.

While she was in hospital profuse sweating and blotching of the skin were observed, and it was found that the blood pressure rose to 160/110 while she was eating. A further sign of cardiovascular lability was shown by the increasing pulse-rate during physical examination. It was then noticed that she produced no tears when she cried. The diagnosis of Riley–Day syndrome was made by Dr. Alex Russell.

Investigations.—These have been repeated many times over several years, and the range of values is given where abnormal.

Haematology: Haemoglobin 58 to 81 per cent.; E.S.R. 27 mm. in 1 hour; white blood count, 31,000 per mm³; polymorphs, 70 per cent. The other investigations confirmed a microcytic anaemia and a response to the chest infection. Repeated tests over the years showed no other abnormalities. No disseminated lupus erythematosus cells. Bone marrow normal.

Biochemistry: Blood urea, 55 mg. per cent.; chloride, 107 mEq./l.; sodium, 140 mEq./l.; potassium, 5·0 mEq./l.; alkaline phosphatase, 15·7 K.A. units; calcium, 10·7 mg. per cent.; phosphatase, 4·8 mg. per cent.; total protein, 8·47–9·35 g. per cent.; albumin, 3·96–5·2 g. per cent.; globulin, 4·51–3·37 g. per cent.; non-protein nitrogen, 29–51 mg. per cent.; transaminases: S.G.O.T., 171–62 μ moles pyruvate/100 ml./hr., S.G.P.T., 115, 65–33 μ moles pyruvate/100 ml./hr.; gamma-globulin turbidity, 12 units; thymol turbidity, 4 units. Paper electrophoresis showed a marked increase in gamma-globulin, while the other proteins were within normal limits. Plasma fatty acid esters, 303 mg. per cent., phospholipids, 9–2 mg. per cent.

Urine: Normal. The screening test for 5-hydroxyindoles was negative. Vanillyl mandelic acid, 0·3 mg./24 hrs.; 17 ketosteroids, 0·54 mg./24 hrs.; 17 ketogenic steroids, 2·4 mg./24 hrs.

Stool: Trypsin detected in dilution of 1 : 60. No occult blood detected.

Sweat: Sodium level below normal.

Bacteriology: No tubercle bacilli were detected. Antistreptolysin titre, 300 units/ml. W.R. negative. G.C.F.T. negative.

Radiology: Chest x-ray: dilated and thickened bronchi seen at both bases, suggestive of bronchiectasis. A little collapse at the right base. Skull: normal. Left wrist: bone age, 6 to 9 years.

E.E.G.: Normal, but in November, 1961, an abnormal E.E.G. of the epileptic type had been recorded.

E.M.G.: No evidence of an active degenerative process.

The abnormal biochemical findings were the raised blood urea, raised non-protein nitrogen in the blood, the high level of transaminases, and the low ketosteroid level.

The child was re-admitted in July, 1962, and in November, 1962, for treatment of the chest infection. In March, 1963, bilateral lengthening of the Achilles tendon was performed for pes equinovarus. In July, 1963, she was admitted with a spontaneous fracture of the femur, and in November, 1963, for a spontaneous fracture of the right tibia. While she was being treated for bronchitis in January, 1963, it was noted that she had bilateral corneal ulcers. She was then referred to the Eye Department. Examination revealed bilateral epithelial abrasions, and scars of previous corneal ulcerations involving Bowman's membrane and the superficial stroma. Refraction showed her to be slightly myopic, and the corrected vision was 6/6 in each eye. Since then she has shown persistent punctate and linear areas on the cornea which stained with fluorescein. These are mainly present on the lower half of the cornea. Corneal sensation was grossly diminished in the right eye, and almost absent in the left. Corneal nerves were visible in the stroma with the slit lamp (× 40). The lenses were clear and the fundi normal.
**Lacrima Response to Various Drugs.**—Schirmer’s test was used with Whatman 41 filter paper, 5 mm. x 5 cm. for 5 minutes in the lower fornix.

<table>
<thead>
<tr>
<th>Date</th>
<th>Schirmer’s Test</th>
<th>Right Eye</th>
<th>Left Eye</th>
</tr>
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<tbody>
<tr>
<td>December 19, 1963</td>
<td>Control</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Injection of pilocarpine 2 mg.</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>February 13, 1964</td>
<td>Control</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Ephedrine tablets, 15 mg.</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>January 2, 1964</td>
<td>Control</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>January 9, 1964</td>
<td>Injection of neostigmine 0·25 mg.</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Injection of adrenaline, 1 min.</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

The pupillary reactions were very variable. On one occasion the pupils were both 7 mm. in diameter and reacted fairly briskly to light but very poorly to accommodation. After 15 minutes they contracted spontaneously to 4 mm. with no change in the illumination of the room, and reacted well to both light and accommodation. Mecholyl 2½ per cent. (acetyl-β-methylcholine) produced no alteration in the pupillary size.

**Discussion**

This child showed most of the typical features of the disease, as described by Riley and others (1949). The features form a distinct entity which appears to be inherited in an autosomal recessive manner. It has been reported in two siblings. The exact mechanism of the production of the symptoms is not clearly understood. Most of the affected functions are under autonomic control, but some, such as the tendon reflexes and the pain response, are not. The abnormality reported in the E.E.G. indicated that both the central nervous system and the peripheral nervous system are involved. There was some evidence of adrenal hypofunction and liver dysfunction.

The production of tears in the normal person is thought to be controlled by the parasympathetic and sympathetic nervous systems. The eye is moistened by the mucous glands of the conjunctiva, by the glands of Krause in the upper lids, and by the “resting” secretion of the lacrimal gland, which may be under the control of the sympathetic nervous system (Duke-Elder, 1932; Whitwell, 1958).

It is believed that the parasympathetic system produces lacrimation in response to psychic or trigeminal nerve stimulation. The pathway from the mid-brain is described as arising in the lacrimal nucleus, travelling in the nervus intermedius of Wrisberg to the tympanic plexus, leaving the tympanic plexus and then passing out of the petrous bone as the greater superficial petrosal nerve. This becomes the nerve of the pterygoid canal and reaches the sphenopalatine ganglion. There it is thought to synapse and the post-ganglionic fibres pass into the zygomatic nerve and then to the lacrimal gland (Mutch, 1944). Post-ganglionic denervation of a gland is said to make the gland more sensitive to the exciting chemical, usually acetylcholine, while pre-ganglionic denervation should not change the sensitivity unless trans-synaptic degeneration occurs. After post-ganglionic denervation the gland should not respond to cholinesterase inhibitors such as Prostigmin. De Haas (1962) reported rather conflicting results from experiments with patients who had had the
facial nerve cut during the removal of acoustic neuromata. He found that the
lacrimal gland appeared to be more sensitive to direct parasympatheticmimetic
agents, even though the denervation was pre-ganglionic. He found little response
to cholinesterase inhibitors.

The child reported here showed a marked response to subcutaneous injections of
pilocarpine, but very little response to Prostigmin, while Kroop (1956) and Pilger
(1957) reported a good response to Prostigmin in patients with this disease. So the
results obtained in this case resemble those described by de Haas, in which the
lesion was pre-ganglionic, but since the results were variable in his cases no definite
conclusions can be drawn. No response at all was elicited by the administration of
adrenaline or ephedrine.

The lack of tear secretion should give rise to the picture of kerato-conjunctivitis
sicca, but no conjunctival changes have as yet been detected. The pre-corneal film
does not appear abnormal, and there are no filaments to be seen on the cornea, but
there is linear and punctate staining in the lower half of the cornea with fluorescein
and Rose Bengal drops. Liebman (1957) stated that active ulceration of the cornea
did not occur after the age of 8 years, but this child had ulcers at the age of 10.

Some of the children develop a condition that is identical with neuroparalytic
keratitis. Sensory denervation of the eye may cause corneal changes of varying
severity. These changes are attributable to an alteration in the metabolism, lack of
response to stimuli, and desiccation of the cornea, the last being thought by many
authors to be an important factor in the development of neuroparalytic keratitis.
Marx (1921) has shown that desiccation occurs more rapidly in anaesthetic than
in normal eyes, but this cannot be the main cause, as neuroparalytic keratitis
can occur after a tarsorrhaphy or in the presence of ptosis. It has been suggested
that the eye is dry because the reflex watering is reduced, but reflex watering is
bilateral, so the normal eye keeps the anaesthetic one moist. The absence of the
blink reflex is also suggested as a cause of neuroparalytic keratitis, but once again,
the blink reflex is bilateral. Many authors believe that the keratitis is due to an
interference with the metabolism of the cornea, which makes it more sensitive to the
effects of drying. Duke-Elder (1938) states: “Desiccation of the cornea results in
the picture of keratitis e lagophthalmo, not in neuroparalytic keratitis”, and other
authorities maintain that neuroparalytic keratitis is entirely due to anaesthesia of
the cornea.

The children suffering from congenital familial dysautonomia may develop either
a neuroparalytic keratitis, a mild keratitis sicca, or no corneal change at all. The
corneal sensation may be absent or severely diminished, but this appears to be part of
a general indifference to pain and not a local phenomenon. No neuroparalytic
changes have been described in other parts of the body, unless the spontaneous
fractures are a manifestation of this. As has been stated, nerves could be seen in
the corneal stroma of this child, which appeared to be normal. Atmospheric
oxygen is normally absorbed by the pre-corneal film and supplies most of the oxygen
requirement of the cornea. This process will be hampered by desiccation and may
contribute to the effect on the corneal metabolism of the anaesthesia. Vitamin-A
deficiency may give a picture rather similar to the corneal changes described, in the
early stages, but its effect is at first more marked in the conjunctiva.
It has been suggested (Smith, Davies, and Breinin, 1964) that Mecholyl drops 2½ per cent. will produce a miosis which is diagnostic in this disease, but no miosis was observed in this child and the pupil reactions were found to be very variable, thus stressing the fluctuations of the activity of the autonomic system which is so characteristic. Mecholyl drops 2½ per cent. are said to produce miosis in Adie's syndrome also. This autonomic instability gives rise to the high morbidity in general anaesthesia (Kritchman and others, 1959). Out of 17 children anaesthetized for ophthalmic procedures, 6 had severe hypotension, and two had cardiac arrest. The child discussed has had several anaesthetics with no untoward reactions.

Alacrimia congenita has been described in association with other lesions. Krüger (1954) reported a family in which a brother and sister had ptosis, distichiasis, conjunctivitis, and keratitis with alacrimia congenita. The father and another brother were said to have defective lacrimation. It was thought to be due to a nuclear defect. Hamilton (1940) reported a case with a right convergent squint and nystagmus. Coverdale (1948) reported a 36-year-old man with no tears and a dry mouth. Children with the Riley–Day syndrome have excessive salivation. The superior salivary nucleus in the pons cerebri is thought to be in very close association with the lacrimal nucleus and its pathway is also via the nervus intermedius to the tympanic plexus, although it then passes into the chorda tympani to the submandibular and sublingual glands. This excessive action of one part of the cranial parasympathetic system and the depression of another underlines the bizarre manifestations of the disease, or perhaps the limitations of our understanding of it. Liebman (1957) described 19 patients, 10 of whom had corneal pathology, 3 with severe neuroparalytic keratitis and 7 with exposure keratitis. He remarked that they tended to sleep with their eyes half-open. Thus, they have three factors which affect the corneae adversely: anaesthesia, exposure, and desiccation.

Differential Diagnosis

Cystic fibrosis of the pancreas may cause confusion in the early stages, but the presence of trypsin in the stools rules this out. I have recently examined the eyes of 55 children with cystic fibrosis of the pancreas and found no corneal changes in any of them. Vitamin-A deficiency may cause a similar ocular picture, but the general manifestations are very different.

Management

This particular child belongs to the group described by Liebman (1957) as having mild corneal changes. Most cases are well controlled with Methyl cellulose drops 1 per cent. or Carboxymethylcellulose drops 1 per cent. several times a day and an oculentum at night. Cauterization of the puncta may be necessary. The management of the patient with neuroparalytic keratitis can be extremely difficult (Dunnington, 1954), and even tarsorrhaphy may not save the sight.

Summary

A case of the Riley–Day syndrome is described. Various methods of inducing lacrimation have been tried. The literature is briefly reviewed.
REFERENCES


