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CONGENITAL GLAUCOMA IN NEONATAL RUBELLA*†‡

BY

M. L. SEARS

From the Department of Surgery, Yale University School of Medicine

A RAISED intra-ocular pressure associated with decreased outflow facility, a progressively enlarging cornea, and atrophy of the optic nerve have been described in neonatal infants born to mothers who acquired rubella during the first trimester of pregnancy (Swan, Tostevin, Moore, Mayo, and Black, 1943; Rones, 1944; Long and Danielson, 1945; Prendergast, 1946; Guerry, 1946; Irvine, 1946; Bardram and Braendstrup, 1947; Zewi, 1948; Hogan, 1958; Waardenburg, Franceschetti, and Klein, 1961; François, 1963; Chandler and Grant, 1965; Alfano, 1966; Costenbader, 1966; Geltzer, Guber, and Sears, 1966; Kaufman, 1966; Maumenee, Monif, Jarrett, Hardy, and Sever, 1966; Roy, 1966; Weiss, Cooper, and Green, 1966).

An analysis of the incidence and characteristics of congenital glaucoma in these patients meets two difficulties:

(1) Does the lesion described meet the diagnostic criteria of congenital glaucoma?

(2) Was the mother really infected with the rubella virus?

The second question can be circumvented by limiting our analysis to those infants who have a diagnosis of rubella substantiated by either positive viral culture or serology (Geltzer and others, 1966).

The first question is not so easily settled because of these factors:

(*i*) The relatively frequent occurrence of corneal opacities, both transient and permanent, mild and severe, in these babies (Gregg, 1941; Auw-Yang Sien, 1951; Swan, 1951; Reese and Ellsworth, 1966; Roy, 1966);

(*ii*) The difficulty of measuring intra-ocular pressure by tactile methods, or even by indentation or applanation tonometry in babies with pathological corneae;

(*iii*) The presence of small or normal-sized opaque corneae which do not enlarge (Long and Danielson, 1945; Swan, 1951; Alfano, 1966; Geltzer and others, 1966; Grant, 1966; Kaufman, 1966; Reese and Ellsworth, 1966);

(*iv*) The apparently ephemeral nature of the raised intra-ocular pressure in some neonatal infants (Long and Danielson, 1945; Waardenburg, and others, 1961; Grant, 1966; O'Neill, 1966; Roy, 1966).

Since the diagnosis of congenital glaucoma has often not been established with

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certainty in many instances, conclusions drawn about the incidence and characteristics of this lesion as well as about the beneficial effects of therapy must be accepted with reservation.

The following observations have been made on a selected population of infants with "congenital glaucoma" drawn from a pooled sample of about 150 neonates with a *proved* diagnosis of rubella in the recent epidemic of 1964–1965.

Incidence

In neonatal infants suspected of affliction with rubella, the incidence of "congenital glaucoma" has been reported to be as high as 25 per cent. (Alfano, 1966). In proven series of neonatal rubella, the incidence varies from 2 to 15 per cent. (Geltzer and others, 1966; O'Neill, 1966; Roy, 1966). If more restrictive criteria are used for the diagnosis of "congenital glaucoma" in this latter group, then an incidence of about 10 per cent. can be estimated.

Physical Findings

The eye with raised intra-ocular pressure appears to take at least three different forms:

(1) The cornea was of normal size or small, and quite diffusely oedematous and opaque. Details of the deeper layers of the cornea were not visible.

(2) The intra-ocular pressure was found to be raised in eyes which had a cornea of normal size which was mildly and diffusely hazy.

(3) The cornea was enlarged with a diffuse haze or clouding and defects in Descemet's membrane.

The corneae of ten of 23 eyes with a diagnosis of congenital glaucoma in infants with known rubella had normal corneal diameters. Three others had corneae not greater than 9 mm. in horizontal diameter. Eight had enlarged corneal diameters. Two showed evidence of descemetocele or perforation after staphyloma formation had occurred; one of these was treated with lamellar keratoplasty and the other was managed with evisceration.

The interior of the eyes in this group could have been examined in fifteen instances, and additional positive findings were described in six (cataract in two, iris transillumination in one, and retinopathy in five).

Considerable numbers of eyes have been described with the lesion of pigmentary retinopathy and/or iris transillumination or thinning in the absence of congenital glaucoma (Marks, 1947; van Alphen, 1951; Emerson, 1958; Gregersen, 1958; O'Neill, 1966; Geltzer and others, 1966). These lesions were not more severe or frequent in eyes with raised intra-ocular pressure.

It should be remembered that the diagnosis of anomalies of the chamber angle in infants is difficult because of the frequent presence of normally increased amounts of uveal tissue in these young eyes (Kupfer, 1963). Rarely is a specific and definite abnormality present. Using strict criteria, gonioscopy revealed three different findings when the chamber angle could be seen:

(*i*) One eye had an irregular anterior insertion of the iris;

(*ii*) Less than half the eyes had finely-dispersed pigment on the surface of the trabeculae. In some instances this pigmentary deposit seemed to disappear since it was not seen in follow-up examinations; in these the iris invariably transilluminated and retinopathy was present.

(*iii*) The remainder had a normal irido-corneal angle.

Positive identification of intra-ocular virus was obtained from culture of eye tissue,

aqueous, or cataract in four eyes. Although culture was not attempted in all eyes, the presence of a positive virus culture in those eyes in which it was done indicates that the virus was probably within the eye in most instances.

Associated Systemic Findings

A wide variety of lesions occurs with raised intra-ocular pressure. A cardiovascular anomaly, usually patent ductus arteriosus, was invariably present.

Diagnosis

The diagnosis of congenital glaucoma usually depends on the reliable demonstration of an increased intra-ocular pressure associated with a decreased outflow facility. The presence of corneal oedema, corneal opacities, or breaks in Descemet's membrane are not necessarily diagnostic of congenital glaucoma since other congenital or neonatally acquired conditions can produce similar corneal pathology (Theodore, 1944; Falls, 1949; Mann, 1957; Reese and Ellsworth, 1966; Speakman and Crawford, 1966).* This is especially true for the acute manifestations of rubella in the newborn. Altered corneal transparency is frequent in these patients and may occur in small or normal-sized corneae without an increase in intra-ocular pressure (Gregg, 1941; Auw-Yang Sien, 1951; Swan, 1951; Reese and Ellsworth, 1966; Roy, 1966). On the other hand, neither is a demonstrated increase on intra-ocular pressure necessarily diagnostic of "congenital glaucoma", unless the increase persists. Several observers have noted transient rises of intra-ocular pressure with spontaneous recovery (Long and Danielson, 1945; Waardenburg and others, 1961; Grant, 1966; O'Neill, 1966; Roy, 1966), while others have examined eyes treated surgically with goniotomy and later have not found the cleft ordinarily felt to be responsible for the normalization of outflow facility and intra-ocular pressure (Grant, 1966; Sears, 1966). Some of the patients with bilateral involvement were treated with goniotomy to one eye only and both eyes were found to be improved on follow-up examinations (Grant, 1966; Roy, 1966).

These observations suggest that in many instances the glaucoma of rubella is an acute process not related to a permanent developmental defect in the chamber angle, but rather to a transient obstruction of outflow of aqueous humour. Studies of rubella in foetuses and tissue culture have in general indicated the presence of virus in affected organs with cellular necrosis but without significant inflammatory response (Boué, Plotkin, and Boué, 1965; Parkman, Phillips, Kirschstein, and Meyer, 1965; Chang, Moorhead, Boué, Plotkin, and Hoskins, 1966; Töndury and Smith, 1966). It is barely possible that the obstruction of aqueous outflow is related to a temporary defect in the development of the trabecular endothelium and/or to temporary deposition of cellular debris over the surface of the trabecular meshwork. The disappearance of cellular debris and the restoration of a normal cameral or trabecular endothelial lining may be associated with a return of intra-ocular pressure to normal. Cellular necrosis may be more extensive in the chamber angles of those eyes which show progressive deterioration. In some few severe instances the pathology of inflammation may create changes in the ciliary body or iris or chamber angle

* The description of anterior chamber anomalies, *i.e.* anterior chamber cleavage syndrome and their synonyms, is beyond the scope of this paper. References to this condition can be found in the papers of Reese and Ellsworth (1966) and Speakman and Crawford (1966).

which interfere with normal aqueous outflow (Wolter, Insel, Willey, and Brittain, 1966; Boniuk and Zimmerman, 1966).

This interpretation is in accord with the evolution of the well-recognized corneal opacity of neonatal rubella. In some instances opacification is permanent, but in others the cornea clears. The corneal endothelium is derived from ingrowing mesenchyme (Mann, 1957). A temporary discontinuity in this layer may occur between the 6th and 8th week. Corneal oedema and opacification result. With restoration of a normal endothelium and its secretory product, Descemet's membrane, the earlier corneal oedema resolves without sequelae.

Further evidence for the acute nature of the neonatal insult by rubella derives from studies of the lens (Cordes and Barber, 1946; Töndury and Smith, 1966). The normal development of the lens begins during the 3rd week with invagination of the surface ectoderm to form a vesicle. By the 6th to 7th week the lens becomes a separate structure. The cavity of the lens vesicle has been obliterated as the posterior cells of the lens differentiate into lens fibre cells. The earliest changes noted in young post-maternal rubella foetuses were damaged fibre cells of the lens which contained pyknotic nuclei with cytoplasmic vacuoles and eosinophilic inclusion bodies. Furthermore, the lens cavity was not obliterated. Finally, the most recently added lens fibres could be seen to be normal at later stages. These findings indicate a certain temporal susceptibility of a sharply-delimited nature as well as the potential for normal cell growth and development at a later stage in maturation.

Although several early descriptions of the occurrence of congenital glaucoma in older than neonatal infants with maternal rubella have appeared in the literature, it is difficult to evaluate these instances. The diagnosis of rubella has not been proved by virological or serological tests. In addition, the time of onset has frequently not been specified. It would seem wise, then, to reserve judgment about the cause and effect relationship between maternal rubella and congenital glaucoma in infants in whom glaucoma appears to begin after the first few months of life.

Therapy

The implication which this analysis has for a therapeutic approach to the problem of rubella glaucoma is clear. It would appear that, in mild cases of corneal oedema associated with raised intra-ocular pressure, a conservative course of medical therapy should be followed unless one can demonstrate progressive alterations in the corneal stroma or in the corneal diameter. Frequent follow-up examinations should include careful repeated measurements of corneal diameter and estimations of the intra-ocular pressure and aqueous outflow facility, if possible. The degree of corneal opacification and its configuration should be carefully recorded. In the meantime, medical treatment in the form of carbonic anhydrase inhibitors and/or topical adrenalin may be helpful. During this period of observation viral cultures and repeated serological testing may help to establish the diagnosis.

If progressive changes in the cornea associated with a persistent elevation of intra-ocular pressure do occur, there are at least three possible surgical choices: goniotomy, filtering procedure, or cyclodiathermy. It is beyond the scope of this paper to discuss the relative merits of these approaches, the choice often depending

on individual preference, but if the chamber angle can be seen, goniotomy is certainly the best procedure.

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