

Infantile glaucoma

Steroid testing in parents of affected children

D. A. LEIGHTON AND C. I. PHILLIPS

Department of Ophthalmology, University of Manchester, and Manchester Royal Eye Hospital

An important hereditary influence in open-angle glaucoma is already known to exist. At present the most powerful means of making manifest the presence of such a trait is probably the application of topical cortisone, which produces a marked rise in ocular tension in susceptible individuals, *i.e.* principally in cases of open-angle glaucoma (Armaly, 1963) and their relatives (Becker and Hahn, 1964). The magnitude and frequency of this rise in open-angle glaucoma has been shown to be greater than in a control sample (Armaly, 1965). Armaly (1966) has also shown that the ocular hypertensive response is itself genetically determined, possibly as a recessive trait.

Since the parents of children with infantile glaucoma are presumably heterozygous for the gene responsible, the condition being recessive, it seemed worthwhile to test their response to topical dexamethasone in order to establish whether or not the carrier state of a gene producing infantile glaucoma shares with open-angle glaucoma the property of a hypertensive response.

Methods

Index patients were thirteen males and five females with infantile glaucoma. Parents of these children were invited to attend for examination. In all, 35 parents (*i.e.* seventeen marital pairs and one mother) were seen and examined at an initial visit, and 28 re-attended after a course of guttae dexamethasone 0.1 per cent. three times a day for 3 weeks.

At the first visit the following procedure was carried out:

- (1) A general, ocular, and family history was taken.
- (2) The optic discs and fundi were examined.
- (3) A slit-lamp examination was performed.
- (4) Applanation tensions, *i.e.* three readings, were taken from each eye, right eye first, the middle reading in order of magnitude being noted.
- (5) The angles were examined with a gonioscope.

Subjects were then given guttae dexamethasone* 0.1 per cent. to be instilled three times daily into one eye for 3 weeks, and were asked to re-attend after that time for repeat applanation tensions. Only 28 out of the possible total of 36 completed the course of guttae dexamethasone. The reasons for this discrepancy are set out overleaf:

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Address for reprints: D. A. Leighton, F.R.C.S., Department of Ophthalmology, Royal Eye Hospital, Manchester, M13 9WH

* This was made up from dexamethasone sodium phosphate, a 0.1 per cent. solution being obtained by the addition of a 0.5 per cent. solution of chlorbutol (Trade name: Decadron, Merck, Sharpe and Dohme Limited).

Number of index patients	18
Total possible number of parents who could be examined	36
Actual number of parents who came for <i>initial</i> assessment (one father did not attend)	35
Number found unsuitable for dexamethasone	1
Number who failed to attend for <i>second</i> visit	6
Total who <i>completed</i> course of dexamethasone	28
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Number who completed course of dexamethasone (28)		males females
12 complete marital pairs	12 12
4 incomplete marital pairs (<i>i.e.</i> only one parent completed tests)	2 2
Total	14 14

24 controls from the Outpatient Department, parents of patients who had squints, were matched for sex and age (within the range +5 to -6 years; the average age difference was minus 0.5 years) with 24 of the parents of affected children, and completed the same course of dexamethasone. It was difficult to achieve 28 controls because defaulting was common after the initial agreement to use dexamethasone.

Results

(1) HISTORY

(a) Consanguinity

Perhaps rather surprisingly, none was noted in any of the parents interviewed.

(b) Family history

In the eighteen families investigated in this way, there were 21 siblings of affected children and none of these had glaucoma. In only one family was there a second affected member and this was an example of dominance or pseudo-dominance (Waardenburg, Franceschetti, and Klein, 1961), the male index patient having had a daughter with unilateral infantile glaucoma.

(2) RESPONSE OF OCULAR TENSION TO GUTTAE DEXAMETHASONE

The mean tension in the test eyes of parents of patients with infantile glaucoma was 16.32 mm. Hg appplanation before and 18.36 mm. Hg after dexamethasone: the corresponding figures for the controls were 15.08 and 18.63 (Table I).

Table I Ocular tension (mm. Hg appplanation) before and after a 3-week course of dexamethasone

Visit	1				2			
	Test		Contralateral		Test		Contralateral	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Series 28 parents	16.32	3.51	16.29	3.33	18.36	3.68	16.11	3.53
24 controls	15.08	3.62	14.92	3.11	18.63	2.89	14.54	4.05

SD = Standard deviation

Of the 28 parents and 24 controls, the tension fell in five and three instances respectively and remained the same in three and one. Inadequate instillation of drops may, of course, be the explanation for the lack of rise in these cases. These differences in the direction of change in tension between parents and controls were statistically non-significant ($\chi^2 = 1.54$; $n = 2$; $0.3 < p < 0.5$).

These observations are shown in the histograms in Figs 1 and 2 as a "shift to the right". The standard deviations before and after treatment were similar.

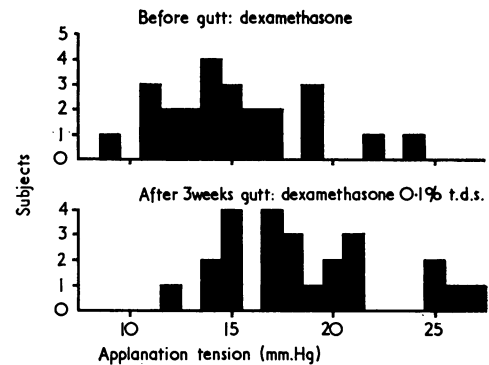
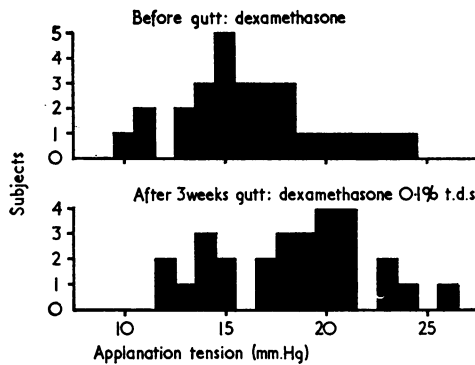


FIG. 1 Applanation tensions of parents of affected children before and after guttae dexamethasone 0.1 per cent. three times daily for 3 weeks. Note a "shift to the right", indicating an ocular hypertensive response, which is quantitatively similar to that in Fig. 2

FIG. 2 Applanation tensions of controls before and after guttae dexamethasone 0.1 per cent. three times daily for 3 weeks. Note a "shift to the right", indicating an ocular hypertensive response, which is quantitatively similar to that in Fig. 1

In a Wilcoxon Matched Pairs Signed Ranks Test (Siegel, 1956), the rise in tension was significant in the parents of affected children and also in the controls ($P < 0.01$) (See Table II).

Table II Statistical analysis of changes in ocular tension (see Table I) of test and control (contralateral) eyes after a 3-week course of dexamethasone (Wilcoxon score)

Eye	Change in ocular tension	Series					
		T	T (0.05)	P	T	T (0.05)	P
(1) Test	Rise	51½	89	< .01*	32	73	< .01*
(2) Test "allowing for change in tension of contralateral eye"	Rise	30	81	< .01*	33	89	< .01*
(3) Contralateral untreated	Fall	118	66	> .05	83	52	> .05

* difference statistically significant ($P < 0.01$).

T (0.05) refers to the Wilcoxon score for a probability of $P = 0.05$ for each test.

Table I shows that, in the contralateral untreated eyes, the ocular tension tended to fall, though not significantly (Table II). This fall in tension of the untreated eye would presumably have been paralleled by a fall in the tension of the test eye if dexamethasone had not been given, and so the fall in the former between Visit 1 and Visit 2 was taken into account in estimating the rise in tension of the test eye after dexamethasone; e.g. if the tension in the contralateral eye had fallen from, say, 13 to 11 mm. Hg between Visits 1 and 2, and the tension in the test eye had risen from 14 to 18 mm. Hg, then the rise in the latter, taking account of the fall in the former, would have been taken as $(4 + 2) = 6$ mm. Hg. A Wilcoxon Test was done on the results expressed in this way between test eyes and untreated eyes in each individual, and again the results were significant for a rise in tension at $P < 0.01$ in both parents and controls (Table II).

However, the magnitude of the rise in pressure in (a) parents as compared with (b) controls did not differ significantly (to a Mann-Whitney U Test (Siegel, 1956) $Z = 1.32$; $U = 264$; $P = 0.0934$). To a Wilcoxon Test, the 24 parents having been carefully matched with 24 of the controls, the absence of a significant difference in the magnitude of the dexamethasone response was confirmed ($T = 88$; T for $P = 0.05$ would have been 66; $P > 0.05$). Similarly, there was no significant sex difference in the response to dexamethasone.

(3) ANGLE OF ANTERIOR CHAMBER

Although one might have suspected that the parents of children with infantile glaucoma would have abnormal tissue in the angles revealing their heterozygous or carrier state, with only one exception, none was present. Angle appearances, therefore, seem to have no value in the detection of the carrier state.

Discussion

No toxic effects of dexamethasone were noted.

The ratio of 18 affected children: 21 normal children in affected families should not be interpreted as favouring a dominant heredity, or as contradicting the generally accepted recessive pattern with a 40 to 60 per cent. penetrance (Waardenburg, Franceschetti, and Klein, 1961). Of the 21 siblings of patients, only two were younger than the index patients. This is probably related to the fact that parents of affected children were informed early in the treatment of their child that, although some cases may not be hereditary, there was statistical evidence that a risk existed to further children of the order of 1 in 8 (recessive gene with 50 per cent. penetrance). If the parents decide that such a risk is too great, only one abnormal child is likely in each family, and this, coupled with the small size of the modern family, must increase the expected 1 : 8 ratio of affected to unaffected children in affected sibships.

The sex ratio of affected children (13 males : 5 females) favours males and this has frequently been found in other series (Shaffer, 1967, mentions 70 per cent.); the sex ratio of their 21 unaffected siblings was 8 males : 13 females. This sex difference was statistically significant ($\chi^2 = 4.55$; $n = 1$; $0.02 < P < 0.05$).

Summary

The response of ocular tension to guttae dexamethasone 0.1 per cent. instilled three times daily for 3 weeks was similar in (a) parents of children with infantile glaucoma and (b) controls who had been closely matched for age and sex.

Accordingly, as judged by the dexamethasone response, the genetic carrier state for infantile glaucoma is not related to open-angle glaucoma.

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