Superior Intelligence in Sighted Retinoblastoma Patients and their Families*

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There are many well-known genetically determined disorders associated with low intelligence, but at least 2 conditions have been reported associated with superior intelligence: retinoblastoma (Thurrell and Josephson, 1966; William, 1968) and the autosomal recessive form of torsion dystonia (Flatau and Sterling, 1911; Eldridge *et al*, 1970). Although proof is still lacking, the superior intelligence noted in the latter trait is thought to be a direct consequence of the specific dystonia gene, whether in single or double dose (Eldridge, 1970).

On the other hand, the higher intelligence noted in children blind from retinoblastoma may have several other explanations. One is that the choice of a suitable comparison group of blind children is difficult. In the above retinoblastoma studies the comparison groups included many children who were congenitally blind. The process producing congenital blindness may also have more general but subtle effects on the central nervous system resulting in decreased intellectual performance. In addition, children with retinoblastoma experience sightedness for several months or longer and this experience may enhance psychomotor growth compared to those who never had such stimulation (Schapiro and Vukovich, 1970). Finally, many patients with retinoblastoma do not survive and those who do may be a select group as suggested by their higher birth weight (Fraser and Friedmann, 1967).

To evaluate the association between retinoblastoma and intelligence while considering these points the following approach was used. Only those patients with retinoblastoma were studied who had useful vision preserved, close relatives affected, and for whom unaffected relatives could be used as controls. By selecting sighted patients as *propositi* the

problem of matching blind controls free of brain damage who once were sighted was avoided. Using close relatives unaffected by retinoblastoma as controls limited the possible socioeconomic bias in referral and survival of retinoblastoma patients.

This approach had the added advantage of possibly reducing the heterogeneity in the patient sample. Retinoblastoma has several causes, germinal or somatic mutation at a single autosomal locus (Ellsworth, 1969) and gross deletion of genetic material on the long arm of a D group chromosome, usually number 13 (Allderdice *et al*, 1969; Orye, Delbeke, and Vandenabeele, 1971) which often produces other anomalies as well. By choosing only patients with positive family history, focus was presumably on the type of retinoblastoma due to germinal mutation.

Methods

Patients who had documented unilateral or bilateral retinoblastoma, vision adequate for reading, and a positive family history were sought through 6 medical centres in the eastern United States. Their families were contacted through the private physician or hospital clinic and a home visit arranged. During the visit the following information was obtained: general medical history, complete genealogy, and brief physical examination with ophthalmological study in appropriate cases. The *propositus*, other affected family members, and unaffected close relatives were given the complete verbal and performance portions of the Wechsler Intelligence Scale for Children and Adults (WISC and WAIS). Two affected adult relatives who were blind as a result of retinoblastoma were given the verbal part of the WAIS but the Stanford-Ohwa-Kohs Block Design Intelligence Test was substituted for the performance part of the WAIS. All children in the study were tested by one of us (K.O'M.) and 2 of us administered all adult tests (K.O. and R.E.). All test results were scored by the same individual (K.O'M.). Individual differences in test performance between each affected person and his control relative were then analysed for significance using a

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TABLE I
RESULTS OF TESTING 23 RETINOBLASTOMA PATIENTS AND THEIR CONTROLS

Family No.	Age (yr)		Sex	Type of Retinoblastoma (eye)	Relationship to Patients	Results					
	Patient	Control				Verbal IQ	Difference	Performance IQ	Difference	Full Scale IQ	Difference
1	39	47	F M	Right	Sib	98 108	-10	92 130	-38	95 118	-23
	8	12	F M	Both	Sib	97 87	+10	101 118	-17	99 102	-3
	11	15	M F	Both	Sib	97 115	-18	120 117	+3	109 117	-8
2	26	54	F M	Left	Father	124 141	-17	132 106	+26	129 128	+1
	19	27	M F	Both	Sib	133 134	-1	146* 132	+14	141 135	+6
3	16	48	M F	Both	Mother	135 124	+11	92 106	-14	118 117	+1
4	13	14	F M	Both	Sib	100 108	-8	117 106	+11	109 107	+2
	36	16	F M	Right	Son	127 115	+12	120 122	-2	125 120	+5
5	40	45	M F	Left	Sib	116 125	-9	92 126	-34	106 127	-21
	11	14	F M	Both	First cousin	129 104	+25	87 108	-21	110 107	+3
6	11	10	M M	Both	Sib	101 91	+10	86 94	-8	93 92	+1
	34	30	M M	Right	Sib	106 121	-15	102 108	-6	105 116	-11
7	8	47	M F	Both	Mother	116 131	-15	104 114	-10	112 125	-13
	8	46	M M	Right	Father	108 119	-11	107 110	-3	108 116	-8
8	39	34	M M	Left	Sib	135 107	+28	125 106	+19	133 107	+26
9	12	16	F M	Both	Sib	116 135	-19	100 101	-1	109 121	-12
	18	21	M M	Right	Sib	127 120	+7	119 110	+9	126 117	+9
10	8	40	F F	Both	Mother	129 104	+25	89 88	+1	111 97	+14
11	12	18	M M	Both	Sib	126 126	0	113 126	-13	122 122	0
	50	37	F F	Right	Sib	124 108	+16	109 110	-1	118 109	+9
12	13	15	F M	Both	Sib	123 111	+12	117 114	+3	122 114	+8
	41	32	F F	Right	Sib	114 116	-2	110 123	-13	113 120	-7
13	19	29	F F	Both	Sib	140 117	+23	152* 93	+59	148 107	+41
Average Patients Controls						118.3 115.9	+2.4	110.1 111.1	-1.0	115.7 114.8	+0.9

* Stanford-Ohrwaki-Kohs Block Design Intelligence Test for the blind.

t test for the mean of independent samples. In addition, an independent observer, unaware of which respondents were affected, also scored all tests and similar differences between each affected and control were obtained.

Results

The charts of approximately 2000 patients treated for retinoblastoma were reviewed at the 6 medical centres. Patients meeting our criteria of preservation of useful vision and positive family history were ascertained through only 2 centres: The Edward S. Harkness Eye Institute of the Columbia Presbyterian Medical Center, New York City and the Wilmer Eye Institute of The Johns Hopkins Hospital, Baltimore. Vital data and test scores of the 23 patients and their controls are given in Table I. Thirteen of the 23 patients had bilateral retinoblastoma. A sib or parent of each patient served as control with the exception of family 5 in which a first cousin was the closest relative available. In 10 instances both patient and control were of the same sex. The average age difference between control and patient was 12.1 years with a median difference of 6.0 years and a range of 0.9 to 38 years. Families 1, 3, 7, 8, and 13 were Jewish, family 6 was American Negro, family 10 was Caribbean Negro, and the remaining 6 were of mixed west European ancestry.

The patient group and the control group of unaffected relatives both obtained significantly higher scores in verbal and performance IQ than the United States average taken as 100 ($p < 0.0001$). However, there was no significant difference between the scores of patients or their controls on the

verbal and performance sections. Comparison of the 11 individual subtests indicated no significant difference in performance on any one although patients tended to do better than their controls in vocabulary and digit span and worse in general information and object assembly.

Discussion

Results of the present study agree in part with 2 earlier studies (Table II). In each study individuals surviving retinoblastoma have an average IQ significantly above that of the general population. However, those surviving retinoblastoma in our series performed no better than controls consisting of unaffected close relatives. In a 4th study recently reported (Witkin *et al*, 1971) patients blind from retinoblastoma performed similarly to congenitally blind and sighted comparison groups in verbal and concentration ability. They differed in perceptual ability, scoring less well than the congenitally blind on a test of tactile embedded figures but higher than both the congenitally blind and sighted comparison groups on tactile block designs.

Because of the possible effect of age and sex on intelligence in our series, separate analysis was made of 11 pairs consisting of a patient and his or her sib of the same sex. The average age difference in these 11 pairs was 0.3 years with a range of -10 to +13 years. Again, no significant difference in performance was noted.

Fifteen of our patients received extensive radiation treatment and chemotherapy. Because of possible subtle cortical brain damage from such therapy producing lowered intellectual functioning,

TABLE II
SUMMARY OF STUDIES ON INTELLIGENCE IN RETINOBLASTOMA (RB)

Study	Source of Patients	No. of RB Patients With Reading Vision	Source of Controls	No. of RB Controls With Reading Vision	Mean IQ, Full Scale (Range)		
					Patients	Controls	Value of p
Thurrell and Josephson (1966)	Wisconsin School for Visually Handicapped	15 (0)	Wisconsin School for Visually Handicapped	15 (0)	120 (65-163)	99 (83-130)	< 0.01
Williams (1968)	All schools for blind in England and Wales	50 (75)	All schools for blind in England and Wales	74 (29)	120	103	< 0.001
			Four Birmingham schools	60 (60)	(110-142)	103	< 0.001
Present study	Two Eastern US medical centres. Propositi had positive family history and useful vision.	23 (21)	First degree relative closest in age to the patient	23 (23)	116 (93-148)	115 (92-135)	

the results were evaluated in terms of therapy received by each patient. A depressing effect was not found. In fact, 10 of the 15 patients so treated had a full-scale performance higher than that of their controls and the average IQ of the 15 was 117 compared to an average of 114 for the 8 not so treated.

Penetrance in retinoblastoma may be 80% or lower (Franceschetti and Bischler, 1946). That is, 20% of the seemingly unaffected children of an affected parent may carry the retinoblastoma gene. Thus, some unaffected sibs used as controls might themselves carry the gene for retinoblastoma. It was possible to avoid this problem altogether for 7 patients for whom a parent married to an affected individual was available as a control. Such a control could not have inherited the retinoblastoma gene from an affected individual. No significant difference was noted in the full-scale IQ or in any subtests in these 7 pairs.

Not included in our results but also evaluated by us were apparent monozygous twins, one of whom had unilateral retinoblastoma and survived while the other was unaffected. Because there was no family history of retinoblastoma they were not included in the main body of this study. The twins were judged to be monozygous on the basis of nearly identical appearance and concordance for all 17 blood group antigens and serum proteins tested. Both scored in the superior range (IQ > 120) and within one point of each other on the WAIS. Since the tumour was unilateral in the affected twin and there was no family history the tumour probably was due to a new mutation which was most likely somatic (Ellsworth, 1969). The observation that both twins, who were probably discordant for the retinoblastoma gene, were similar in psychometric performance provides further evidence that the presence of the mutant gene does not in itself confer intellectual advantage.

The findings in this report suggest that the increased intellectual performance noted in retinoblastoma survivors is probably not the primary consequence of their carrying the gene for retinoblastoma. Rather it is a reflection of the high intelligence of families with retinoblastoma survivors in this series.

These observations may have several explanations. Bright individuals may be more likely to produce children with retinoblastoma. Perhaps this is because their schooling is longer and pregnancies are delayed while formal training is completed. Increased parental age predisposing to such mutation has been noted in retinoblastoma (Fraser and Friedmann, 1967). Alternatively, there may be a selection process involved in diagnosis, referral to

special centres, and treatment resulting in a surviving group which is significantly brighter than the average. Consistent with this possibility is the observation in one series that the average birth weight is higher in survivors than in those who died with retinoblastoma (Fraser and Friedmann, 1967). Birth weight is related to socioeconomic status and with intelligence (Churchill, Neff, and Caldwell, 1966). The observation that Blacks with retinoblastoma have approximately 2½ times the mortality rate of Whites in the United States suggests that there are significant differences in chances for survival depending on socioeconomic status (Jensen and Miller, 1971). Survival with useful vision likely involves even greater selection.

Summary

The psychometric function of 23 sighted patients with retinoblastoma who had a positive family history was determined. Comparison was made with a close, unaffected relative of each.

There was no significant difference between the 2 groups in overall function or on the verbal and performance subsections. However, the average overall IQ scores of the patients (116) and controls (115) were both significantly above the average in the United States taken as 100.

Since close relatives who are unaffected with retinoblastoma are also bright, it is unlikely that the high intelligence present in retinoblastoma survivors is due to the gene for retinoblastoma. More likely possibilities are that retinoblastoma is more frequent in bright families or that a patient with retinoblastoma is more likely to survive if born into a bright family, or both.

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REFERENCES

- Allderdice, P. W., Davis, J. G., Miller, O. J., Klinger, H. P., Warburton, D., Miller, D. A., Allen, Jr., F. H., Abrams, C. A. L., and McGilvray, E. (1969). The 13 q- deletion syndrome. *American Journal of Human Genetics*, **21**, 499-512.
- Churchill, J. A., Neff, I. W., and Caldwell, D. F. (1966). Birth-weight and intelligence. *Obstetrics and Gynecology*, **28**, 425-429.
- Eldridge, R. (1970). The torsion dystonias: literature review, genetic and clinical studies. *Neurology*, **20**, no. 11, Suppl., part 2, pp. 63-65.

- Eldridge, R., Harlan, A., Cooper, I. S., and Riklan, M. (1970). Superior intelligence in recessively inherited torsion dystonia. *Lancet*, **1**, 65-67.
- Ellsworth, R. M. (1969). The practical management of retinoblastoma. *Transactions of the American Ophthalmological Society*, **67**, 462-534.
- Flatau, E. and Sterling, W. (1911). Progressiver Torsionsspasmus bei Kindern. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, **7**, 586-612.
- Franceschetti, A. and Bischler, V. (1946). Rétinoblastome et hérédité. *Archiv der Julius Klaus-Stiftung für Vererbungsfor-schung, Sozialanthropologie und Rassenhygiene*, **21**, 322-328.
- Fraser, G. R. and Friedmann, A. I. (1967). Retinoblastoma. In *The Causes of Blindness in Childhood*, pp. 35-42. Johns Hopkins Press, Baltimore.
- Jensen, R. D. and Miller, R. W. (1971). Retinoblastoma: epidemio-logic characteristics. *New England Journal of Medicine*, **285**, 307-311.
- Orye, E., Delbeke, M. J., and Vandenabeele, B. (1971). Retino-blastoma and D-chromosome deletions. *Lancet*, **2**, 1376.
- Schapiro, S. and Vukovich, K. R. (1970). Early experience effects upon cortical dendrites: A proposed model for development. *Science*, **167**, 292-294.
- Thurrell, R. J. and Josephson, T. S. (1966). Retinoblastoma and intelligence. *Psychosomatics*, **7**, 368-370.
- Williams, M. (1968). Superior intelligence of children blinded from retinoblastoma. *Archives of Disease in Childhood*, **43**, 204-210.
- Witkin, H. A., Oltman, P. K., Chase, J. B., and Friedman, F. (1971). In *Cognitive Studies*, vol. 2, ed. J. Hellmuth, pp. 16-46. Brunner/ Mazel, New York.