AOS THESIS

Depression, Anxiety, and Stress in Parents of Patients With Retinoblastoma

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• PURPOSE: To assess depression, anxiety, and stress in parents of patients with retinoblastoma and to evaluate the impact of unifocal vs multifocal retinoblastoma.

• METHODS: A cross-sectional, self-reported psychological assessment of parents of patients with retinoblastoma at a tertiary care ocular oncology center was performed. The Beck Depression Inventory–II (BDI), Beck Anxiety Inventory (BAI), The Parental Stress Index 4–Short Form, and a retinoblastoma Knowledge Assessment questionnaire were administered. Descriptive statistics for outcomes and comparative analyses were made.

• RESULTS: There were 138 parents of children with retinoblastoma (unifocal: n = 77, multifocal: n = 61). Overall, parents displayed mild, moderate, or severe depression (BDI) (n = 37, 26.7%); mild, moderate, or severe anxiety (BAI) (n = 49, 35.8%), and stress scores within normal limits (n = 138, 100%). A comparison (unifocal vs multifocal) revealed parents of children with multifocal retinoblastoma with severe depression (1.4% vs 10.2%, $P < .02$), and no differences in anxiety or stress. Factors associated with moderate or severe parental depression included previous history of depression (30.0% vs 3.9%, $P < .001$) and factors for moderate or severe anxiety included previous history of depression (33.3% vs 8.6%, $P < .001$), parent highest level of education at high school or less vs college or beyond (29.2% vs 10.9%, $P = .031$), and parental report of "child developmental delay" (31.5% vs 11.3%, $P = .019$).

• CONCLUSIONS: The majority of parents displayed minimal depression (73.3%), anxiety (64.2%), or stress (100%). However, severe depression is more often found in those whose children have multifocal disease, and previous history of depression and less education can impact psychological function. NOTE: Publication of this article is sponsored by the American Ophthalmological Society. (Am J Ophthalmol 2019;207:130–143.

RETINOBLASTOMA IS THE MOST FREQUENT PRIMARY intraocular cancer in children, affecting nearly 8000 children worldwide.[1,2] Approximately 250–300 new cases per year occur in the United States, and although it is rare, that number is similar to figures regarding other central nervous system (CNS) tumors in children aged less than 1 year (CNS tumors 41.9, retinoblastoma 32.2 per 1 000 000 population).[3] Retinoblastomas can occur in 2 forms: those with a single tumor in 1 eye (unilateral, unifocal retinoblastoma), or those with multiple tumors in 1 or both eyes (bilateral or unilateral, multifocal retinoblastoma). It is a disease of young children, with most patients diagnosed within the first 2 years of life. In a recent review of all cases of retinoblastoma in an epidemiologic database, patients with bilateral retinoblastoma were diagnosed at an average age of 0.46 years while those with unilateral disease averaged 1.77 years.[4]

In the United States, treatment of retinoblastoma is usually curative and lifesaving. Treatment may consist of surgical removal of the afflicted eye or eyes, radiotherapy, chemotherapy (intravenous, intra-arterial, and intravitreal routes), laser photocoagulation, thermotherapy, and/or cryotherapy.[5,6] The use of both external beam and plaque radiotherapy has declined over recent years. A majority of the patients with regressed retinoblastoma following treatment will have ophthalmic issues such as impaired or absent vision, and additional cosmetic deformities. Only a few will be able to achieve relatively normal vision.

Retinoblastoma is caused by a germline RB1 gene mutation in all patients with bilateral disease, and in 15% of those with unilateral disease.[7] Further, those with unilateral, multifocal retinoblastoma always carry the germline RB1 mutation. Despite the fact that cure rates of the initial cancer approach 95%–99% in developed countries,[8] important implications owing to the genetics of retinoblastoma include: a risk of the disease in other family members, an approximate 50% risk of retinoblastoma in children of

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germline retinoblastoma survivors, and the known risk of survivors developing other nonretinoblastoma cancers later in life.[9–15]

Epidemiologic studies on survival have shown greater mortality for patients with germline mutation (presenting either with bilateral retinoblastomas or with unilateral, multifocal tumors), demonstrating 10-year survival of 90.3% for those with bilateral retinoblastoma compared to 96.1% for those with unilateral tumors.[4] The risk of secondary malignancies at 10 years in this cohort showed a significant difference between the bilateral (7.8%) and unilateral (1.3%) patients. Other published studies examining the risk of secondary malignancies in patients with retinoblastoma have demonstrated significantly higher risk in patients with germline mutation,[9] with increased risk of death from these second cancers.[16] It has been further noted that retinoblastoma patients who survive a second nonocular tumor are at even higher risk for subsequent new tumors than they were for the secondary malignancy.[17] Recent long-term surveillance studies of retinoblastoma survivors have revealed a higher overall mortality in patients with hereditary (germline mutation) retinoblastoma, but no significantly elevated mortality risks were seen in nonhereditary (somatic mutation) retinoblastoma survivors.[13,18,19]

Most studies on retinoblastoma focus on therapeutic outcomes. There have been few studies to examine the precise psychological impact of this cancer on retinoblastoma survivors or their parents. Such a study is unique because it must consider the issues of germline mutation (hereditary retinoblastoma) in some of the patients, the fact that the parent or other family member may have had the disease, the potential risk for disease in future siblings, and the reality that survivors are considered as having a chronic illness. These issues make retinoblastoma different from other chronic illnesses that lack genetic factors and different from other cancers, where a cure results in a low risk of a second malignancy following primary therapy.

STATEMENT OF PURPOSE AND HYPOTHESIS

THIS IS THE FIRST COMPREHENSIVE ASSESSMENT OF PSYCHOlogical functioning of parents of newly diagnosed and treated patients with retinoblastoma. The study includes examination of possible risk factors that may contribute to higher levels of depression, anxiety, and stress in these parents.

The primary outcomes are to establish the levels of depression, anxiety, and stress in parents of patients with unifocal retinoblastoma; to compare those levels with parents of patients with hereditary, multifocal disease; and to establish the knowledge base of parents of patients with retinoblastoma to determine whether that knowledge affects parental depression, anxiety, and stress levels. Secondary outcomes include establishing risk factors for increased depression, anxiety, and stress levels in this parent cohort.

The hypothesis for this thesis is that parents of children with multifocal, hereditary retinoblastoma have increased depression, anxiety, and stress levels compared with parents of children with unifocal, nongermline retinoblastoma. Retinoblastoma is unique in that there are multiple issues that contribute to the psychological impact of the disease, including that in the hereditary form, even when the primary tumors are cured, the patient has a lifelong risk for secondary malignancy. Understanding the psychological impact of this disease on parents of affected children in both the unifocal and multifocal forms is important for the clinician to provide optimal care to the patient and family.

METHODS

INSTITUTIONAL REVIEW BOARD APPROVAL WAS OBTAINED, and the study was then conducted in accordance with the principles of the Declaration of Helsinki and conformed to the United States Health Insurance Portability and Accountability Act regulations. All subjects signed an informed consent form.

All parents (or legal guardians) of patients with retinoblastoma presenting to the Wills Eye Hospital Ocular Oncology Service over a 14-month period were approached for possible inclusion in the study. Informed consent was obtained. Parents or legal guardians of both newly diagnosed and previously treated patients with retinoblastoma were included with the intention of establishing baseline psychological functioning data for all parents of patients being treated or monitored for retinoblastoma. A demographic form, Beck Depression Inventory–II (BDI),[20,21] Beck Anxiety Inventory (BAI),[22] The Parental Stress Index 4–Short Form (PSI 4-SF),[23,24] and a retinoblastoma Knowledge Assessment questionnaire were administered to each parent (or legal guardian) at enrollment. The timing of the completion of the forms was standardized; the parent (or legal guardian) was given the forms by an informed retinoblastoma management assistant in the preoperative waiting room and before the child underwent examination under anesthesia. The parent completed the forms, and these were collected by the assistant prior to the ophthalmologist discussing the results of the examination with the parent. This was routine in all cases. If 2 parents or legal guardians were present, only 1 parent independently completed the survey forms. Both parents were not allowed to fill out forms for the same child.

Study inclusion criteria included parents or legal guardians of patients diagnosed with retinoblastoma at age 0 to 12 years, 11 months. These parents and legal guardians were required to be able to provide informed consent. Candidates for the study were required to speak fluent English, as the surveys were designed and validated for English speakers living in the western world.

TABLE 1. Evaluation of Parent and Child Features

Category	All Patients N = 138	Unifocal Retinoblastoma N = 77	Multifocal[a] Retinoblastoma N = 61	*P* Value
Parent (guardian) features				
Parent relationship to the child (%)				
Mother	72.8	75.0	70.0	.69
Father	25.0	22.4	28.3	
Legal guardian	2.2	2.6	1.7	
Parent age at time of survey (y), mean (SD)	34.6 ± 6.5	34.9 ± 6.7	34.2 ± 6.4	.55
Parent ethnic identity (%)				
White	66.9	67.1	66.7	.96
Other (Black, Hispanic, Asian)	32.8	32.9	33.3	
Parent marital status (%)				
Married	77.2	82.9	70.0	.044
Not married	22.8	19.4	30.0	
Parent highest level of education (%)				
High school or less	17.6	15.8	20.0	.52
College or beyond	82.4	84.2	80.0	
Parent history of depression (% yes)	22.1	25.0	18.3	.35
Family history of retinoblastoma (% yes)				<.001
Parent	16.3	3.8	31.3	
Sibling	2.0	0	4.5	
Other	0.68	0	1.5	
Affected child features				
Affected child age at diagnosis of retinoblastoma (mo), mean (SD)	15.4 ± 17.8	20.5 ± 20.7	9.2 ± 10.5	<.001
Child developmental delay (% yes)	14.0	9.2	20.0	.071
Child genetic testing				<.001
Yes, germline (%)	45.6	24.0	72.1	
Yes, somatic (%)	34.6	60.0	3.3	
No, not performed (%)	19.9	16.0	24.6	
Interval diagnosis to interview (%)				
At time of diagnosis	5.3	4.1	6.7	.73
≤6 months	20.3	21.9	18.3	
7–12 months	11.3	11.0	11.7	
13–24 months	20.3	23.3	16.7	
>24 months	42.9	39.7	46.7	
Time since last treatment (%)				.69
Currently being treated	30.3	32.7	27.8	
≤6 months	14.7	12.7	16.7	
7–12 months	7.3	9.1	5.6	
13–24 months	12.8	9.1	16.7	
>24 months	34.9	36.4	33.3	

Pearson χ^2 test for categorical variables and *t* test for continuous variables.
[a]All multifocal cases were bilateral.

As is routine in our ocular oncology practice, all families were counseled at the initial visit and at each follow-up visit by the ocular oncologist and the pediatric oncologist regarding risk of germline mutation, including multifocality of disease, risk for pinealoblastoma and other CNS malignancies, second cancers, and risk for transmission to further siblings and progeny. Counseling was done following the examination or the examination under anesthesia. Genetic analysis was offered in all cases, but not all parents accepted genetic testing. In patients in whom genetic testing was completed, the ocular oncologist relayed results to the family.

• **DEMOGRAPHIC SURVEY:** Demographic details collected by survey of the parent enrolled in the study include parent and child sex, age, and ethnicity as well as parent marital status, parent highest education level, zip code, parent history of depression/anxiety as determined by a physician,

TABLE 2. Retinoblastoma Treatment Features

Feature	All Patients N = 138	Unifocal Retinoblastoma N = 77	Multifocal[a] Retinoblastoma N = 61	*P* Value
Systemic chemotherapy (%)	56.0	29.5	88.9	<.001
Intra-arterial chemotherapy (%)	56.7	65.4	46.0	.02
Enucleation (%)				.73
One eye	22.0	23.1	20.6	
Both eyes	0	0	0	
Laser thermotherapy (%)	38.3	17.9	63.5	<.001
Cryotherapy (%)	33.3	17.9	52.4	<.001
Intravitreal chemotherapy (%)	22.0	23.1	20.6	.73
External beam radiotherapy (%)	2.8	1.3	4.8	.22
Plaque radiotherapy (%)	7.1	7.7	2.8	.76
Total number of treatments (mean ± SD)	3.0 ± 1.6	2.1 ± 1.2	4.1 ± 1.3	<.001

Pearson χ^2 test for categorical variables and *t* test for continuous variables.
[a]All multifocal cases were bilateral.

and the child's history of developmental delay as determined by a physician.

Disease-associated medical information was collected by chart review of the patient's ocular oncology record. This information included the presence or absence of a family history of retinoblastoma, whether the child had undergone genetic testing, presence of a germline or somatic mutation as determined by genetic testing, interval time between study enrollment and initial retinoblastoma diagnosis, interval time between study enrollment and most recent retinoblastoma treatment, and whether the

TABLE 3. Parental (Guardian) Psychological Assessment of Depression, Anxiety, and Stress in 138 Cases of Unifocal vs Multifocal Retinoblastoma

Psychological Assessment	All Parents N = 138	Parents of Patients With Unifocal Retinoblastoma N = 77	Parents of Patients With Multifocal Retinoblastoma N = 61	*P* Value
Beck Depression Inventory category[a] (%)				
Minimal	73.3	72.2	74.6	.76
Mild	16.8	19.4	13.6	.37
Moderate	4.6	6.9	1.7	.15
Severe	5.3	1.4	10.2	.026
[2]Beck Anxiety Index category[b] (%)				
Minimal	64.2	63.2	65.6	.77
Mild	21.2	25.0	16.4	.22
Moderate	8.0	6.6	9.8	.49
Severe	6.6	5.2	8.2	.49
Parenting Stress Index 4–Short Form[c] (%) (T score mean ± SD)[d]				
Parental Distress	46.3 ± 9.4	45.7 ± 8.9	47.1 ± 9.9	.38
Parent-Child Dysfunctional Interaction	43.5 ± 7.0	42.8 ± 6.7	44.2 ± 7.3	.25
Difficult Child	44.7 ± 9.4	45.1 ± 9.9	44.1 ± 8.8	.54
Total Stress Score	44.6 ± 8.1	44.4 ± 8.1	44.7 ± 8.0	.80

Pearson χ^2 test for categorical variables and *t* test for continuous variables.
[a]Beck Depression Inventory–II; a total score of 0–13 indicates minimal depression; 14–19, mild depression; 20–28, moderate depression; and 29–63, severe depression.
[b]A total score of 0–7 indicates minimal anxiety; 8–15, mild anxiety; 16–25, moderate anxiety; and 26–63, severe anxiety.
[c]A score <85% is considered within normal range.
[d]T scores are calculated for each normative group using a nonnormalized linear transformation of raw scores. Raw score to T-score conversion tables for PSI 4 domain and subscale scores are provided in Appendix B of the official Parenting Stress Index manual.[24]

TABLE 4. Knowledge Assessment for Parents' Understanding of Retinoblastoma Facts

Questions	% Correct			*P* Value
	All Patients N = 138	Unifocal Retinoblastoma N = 77	Multifocal Retinoblastoma N = 61	
Total score (mean % correct, SD)	70.2 ± 20.8	72.4 ± 21.3	67.4 ± 19.9	.17
1. Retinoblastoma is a tumor in the eye that causes a loss of sight but will not spread.	91.7	91.8	91.7	.98
2. Treatments for retinoblastoma include chemotherapy, laser, and enucleation (surgery to remove the eye).	97.0	97.2	96.7	.84
3. If a child has retinoblastoma in both eyes, they have a 50% chance of passing it along to their child.	72.9	68.4	78.3	.20
4. If a child has retinoblastoma in only one eye, they have a 50% chance of passing it along to their child.	46.6	56.2	35.0	.015
5. There are two forms of retinoblastoma: hereditary and sporadic.	93.9	94.5	93.2	.76
6. If a child has hereditary retinoblastoma, they have an increased risk of brain, bone, and skin tumors.	75.2	82.2	66.7	.039
7. If a child has sporadic retinoblastoma, their risk of another tumor at some point in their life is more than 30%.	29.3	37.0	20.0	.032

Pearson χ^2 test for categorical variables and *t* test for continuous variables.
Correct answers are 1. False, 2. True, 3. True, 4. False, 5. True, 6. True, 7. False.

treatment history included only a single treatment or was multimodal.

• **BECK DEPRESSION INVENTORY:** The BDI[20,21] was designed as a screening tool to assess the intensity of depression in adults. Its diagnostic thresholds are in keeping with the depression criteria published in the *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition*. It is validated for use in persons 13–80 years of age. The test is used to assess depression in clinical and research settings and can be self-administered or verbally administered by a trained administrator. It consists of 21 questions and takes approximately 5 minutes to complete. Each item is a list of several statements arranged in increasing severity about a particular symptom of depression. A total score of 0–13 indicates minimal depression; 14–19, mild depression; 20–28, moderate depression; and 29–63, severe depression. Scores above the minimal level are considered clinically relevant, and moderate and severe scores may warrant timely intervention.

• **BECK ANXIETY INVENTORY:** The BAI[22] is a well-validated screening tool used to measure anxiety levels in adults aged 17–80 years. The tool distinguishes between anxious and nonanxious diagnostic groups in a variety of clinical populations. Included in the suggested uses of this test are assessments of anxiety in clinical and research settings. It can be self-administered or verbally administered by a trained administrator and takes approximately 5–10 minutes to complete. It is a 21-question multiple-choice self-report inventory that is used to measure the severity of anxiety. The questions address symptoms of anxiety that the subject may have experienced during the past week. Each answer is scored on a scale of 0 (not at all) to 3 (severely). Higher total scores indicate more severe anxiety symptoms. Total score of 0–7 indicates normal to minimal anxiety; 8–15, mild anxiety; 16–25, moderate anxiety; and 26–63, severe anxiety.[22] Scores above the minimal level are considered clinically relevant, and moderate and severe scores may warrant timely intervention.

• **PARENTING STRESS INDEX 4–SHORT FORM:** The PSI 4-SF[23] is a well-validated 36-item screening tool used to identify parents experiencing high stress levels owing to their parenting roles. The items are divided into 3 domains: Parental Distress (PD), Parent-Child Dysfunctional Interaction (P-CDI), and Difficult Child (DC). These combine to form a Total Stress scale, which measures the overall stress a parent feels within the parental role. The subscales are further described as follows: PD: level of distress a parent is experiencing from factors directly related to parenting; P-CDI: the parent's perception that the child does not meet his or her expectations, which may cause

TABLE 5. Beck Depression Index Scoring per Parent (Guardian) and Affected Child: Analysis of Related Factors

Beck Depression Index Scoring[a]	% Minimal/ Mild	% Moderate/ Severe	*P* Value
Parent (guardian) features			
Parent relationship to the child			.082
Mother	87.3	12.7	
Other	97.3	2.7	
Parent marital status			.14
Married	92.1	7.9	
Not married	82.8	17.2	
Parent highest level of education			.52
High school or less	85.0	15.0	
College or beyond	90.9	9.1	
Parent history of depression			<.001
Yes	70.0	30.0	
No	96.1	3.9	
Affected child features			
Child developmental delay			.36
Yes	83.4	17.3	
No	91.1	8.9	
Family history of retinoblastoma			.96
None	89.9	10.2	
Parent or sibling	90.0	10.0	
Child genetic testing			.53
Germline	90.4	9.6	
Somatic	93.0	7.0	
Interval diagnosis to interview			.71
≤6 months	91.4	6.7	
>6 months	89.2	10.8	
Time since last treatment			.90
≤6 months	92.0	8.0	
>6 months	91.3	7.0	
Treatment history			.30
Single treatment	93.5	6.5	
Multimodal	88.4	11.6	

Pearson χ^2 test for categorical variables.

[a]Beck Depression Inventory–II; a total score of 0–13 indicates minimal depression; 14–19, mild depression; 20–28, moderate depression; and 29–63, severe depression.

TABLE 6. Beck Anxiety Index Scoring per Parent (Guardian) and Affected Child: Analysis of Related Factors

Beck Anxiety Index Scoring[a] Feature	% Minimal/ Mild	% Moderate/ Severe	*P* Value
Parent (guardian) features			
Parent relationship to the child			.89
Mother	85.5	14.5	
Other	86.5	13.5	
Marital status			.72
Married	86.4	13.6	
Not married	83.8	16.2	
Parent highest level of education			.031
High school or less	70.8	29.2	
College or beyond	89.1	10.9	
Parent history of depression			<.001
Yes	66.7	33.3	
No	91.4	8.6	
Affected child features			
Child developmental delay			.019
Yes	68.5	31.5	
No	88.7	11.3	
Family history of retinoblastoma			.72
None	84.9	15.1	
Parent or sibling	85.9	14.1	
Child genetic testing			.11
Germline	91.2	8.8	
Somatic	80.4	19.6	
Time since diagnosis			.62
≤6 months	83.3	16.7	
>6 months	86.7	13.3	
Time since last treatment			.83
≤6 months	86.0	14.0	
>6 months	87.5	12.5	
Treatment history			.37
Single treatment	80.6	19.4	
Multimodal	86.7	13.3	

Pearson χ^2 test for categorical variables.

[a]Beck Anxiety Inventory; a total score of 0–7 indicates minimal anxiety; 8–15, mild anxiety; 16–25, moderate anxiety; and 26–63, severe anxiety.

the parent to project the feeling that the child is a negative element in his or her life; DC: temperament and behavior of the child that influences how difficult or easy the child is to manage. Each of the 36 items is graded on a 5-point Likert scale, from 1 (strongly disagree) to 5 (strongly agree). PSI scores less than the 85th percentile are considered within the normal range, scores between the 85th and 90th percentile are considered high, and scores above the 90th percentile are viewed as clinically significant for parental stress.[24]

• KNOWLEDGE ASSESSMENT: The Knowledge Assessment survey was developed by the study authors, each of whom have extensive clinical experience with this population, to evaluate the knowledge base of each parent regarding retinoblastoma and its associated risks. It was designed in a True-False format and consists of 7 questions that the authors believe parents of children with retinoblastoma should be able to answer correctly if they are fully informed about the disease. The questions include items that assess parent knowledge about the possibility of the retinoblastoma tumor spreading

TABLE 7. Parenting Stress Index 4–Short Form Scoring for Parent (Guardian) and Affected Child Based on Demographics and Clinical Features

PSI Scoring[a] Feature	Parental Distress (PD) (T Score[b] ± SD)	Parent-Child Dysfunctional Interaction (P-CDI) (T Score[b] ± SD)	Difficult Child (DC) (T Score[b] ± SD)	Total Stress Score (TSS) (T Score[b] ± SD)
Parent (guardian) features				
Parent relationship to the child				
Mother	47.4 ± 9.5	43.5 ± 6.6	45.1 ± 8.7	44.9 ± 7.5
Other	43.2 ± 8.2	43.6 ± 8.5	43.75 ± 10.1	43.6 ± 9.3
P value	.001	.95	.48	.43
Parent marital status				
Married	46.5 ± 9.5	43.8 ± 7.3	44.6 ± 9.4	44.7 ± 8.3
Not married	45.3 ± 8.8	42.8 ± 6.7	44.8 ± 9.3	43.8 ± 7.6
P value	.51	.51	.90	.55
Parent highest level of education				
High school or less	45.5 ± 7.6	43.8 ± 6.1	46.8 ± 8.8	44.9 ± 6.3
College or beyond	46.3 ± 9.6	43.4 ± 7.4	44.3 ± 9.4	46.2 ± 11.1
P value	.67	.78	.23	.42
Parent history of depression				
Yes	51.8 ± 10.6	46.4 ± 6.7	47.9 ± 8.6	48.7 ± 7.8
No	44.5 ± 8.2	42.6 ± 7.1	43.8 ± 9.4	43.3 ± 7.8
P value	.001	.009	.025	.001
Affected child features				
Child developmental delay				
Yes	47.6 ± 7.3	49.2 ± 6.3	50.2 ± 8.8	48.8 ± 5.2
No	46.0 ± 9.6	42.6 ± 6.9	43.8 ± 9.2	43.9 ± 8.3
P value	.40	<.001	.007	.001
Family history of retinoblastoma				
None	46.6 ± 9.3	43.8 ± 7.2	45.2 ± 9.5	45.0 ± 8.2
Parent or sibling	43.8 ± 9.4	42.5 ± 7.5	42.2 ± 8.6	42.1 ± 7.8
P value	.20	.49	.15	.12
Child genetic testing				
Germline	46.8 ± 9.3	44.5 ± 8.0	44.3 ± 8.4	44.8 ± 7.8
Somatic	45.6 ± 8.8	42.5 ± 5.5	45.2 ± 9.4	43.9 ± 7.4
P value	.49	.12	.60	.55
Interval diagnosis to interview				
≤6 months	44.6 ± 7.8	42.0 ± 4.9	40.8 ± 6.5	42.5 ± 6.4
>6 months	46.9 ± 9.8	44.3 ± 7.6	45.9 ± 9.8	45.2 ± 8.5
P value	.18	.005	.001	.05
Time since last treatment				
≤6 months	46.0 ± 10.0	42.6 ± 5.2	42.7 ± 7.9	43.6 ± 7.5
>6 months	47.2 ± 9.4	44.5 ± 8.6	46.6 ± 10.4	45.7 ± 8.8
P value	.43	.10	.011	.12
Treatment history				
Single treatment	46.2 ± 8.8	45.8 ± 8.1	47.2 ± 12.0	46.9 ± 9.5
Multimodal	46.4 ± 9.6	42.7 ± 6.7	43.8 ± 8.3	43.8 ± 7.5
P value	.90	.05	.14	.09

PSI = Parenting Stress Index.

t test for continuous variables.

[a]A PSI score <85% is considered within normal range.

[b]T scores are calculated for each normative group using a nonnormalized linear transformation of raw scores. Raw score to T-score conversion tables for PSI 4 domain and subscale scores are provided in Appendix B of the official Parenting Stress Index manual.[24]

beyond the eye, treatment options, heritability of bilateral and unilateral retinoblastoma, and the increased risk of secondary tumors in patients with hereditary (familial) or sporadic retinoblastoma.

• **BIOSTATISTICS:** This is a cross-sectional, self-reported study of the psychological functioning of parents of patients with retinoblastoma. Descriptive statistics are used to report the results in multiple domains of psychological

functioning. Furthermore, they are used to summarize the respondent characteristics and parents' self-report of psychosocial and knowledge outcomes including parental depression, anxiety, stress, and knowledge of retinoblastoma.

Several comparisons are of interest in this study. First, parents of multifocal retinoblastoma patients are compared to parents of unifocal retinoblastoma patients. We also compare disease knowledge among parents of patients to assess the potential impact of this knowledge on psychological functioning. Lastly, for specific outcomes, normative data (population-based data) are used for comparison, with appropriately adjusted models.

Tests comparing demographic variables between parents of bilateral and unilateral retinoblastoma patients were performed by using 2-tailed *t* test for continuous variables and Pearson χ^2 test for categorical variables. For variables with more than 2 continuous categories, such as time since diagnosis, an analysis of variance was used. We then compared depression, anxiety, and stress (as measured by the survey results) among parents of patients with multifocal vs unifocal retinoblastoma. Lastly, we compared each of the psychosocial functioning tools to each demographic variable in order to identify any potential confounders. Statistical tests were performed using Microsoft Excel Version 14.1.4 (Microsoft Corp, Redmond, Washington, USA) and StatPlus v6 (AnalystSoft, Walnut, California, USA).

RESULTS

• **PARTICIPANTS:** There were a total of 138 parents/legal guardians of 138 patients with retinoblastoma who met inclusion criteria and were enrolled in this study. The patients were affected by unifocal retinoblastoma, (n = 77, 56%) or multifocal retinoblastoma (n = 61, 44%). The parent and affected child demographics are summarized in Table 1. The majority of study enrollees were mothers (n = 99, 72%), with a similar distribution among the unifocal (n = 57, 75%) and multifocal (n = 42, 70%) groups. A comparison (unifocal vs multifocal retinoblastoma) revealed differences in parental marital status as married (82.9% vs 70%, $P = .04$), family history of retinoblastoma in parent (3.8% vs 31.3%, $P < .001$), affected child age at time of diagnosis (20.5 vs 9.2 months, $P < .001$), and presence of a germline mutation (24% vs 72.1%, $P < .001$). The presence of developmental delay in the affected child demonstrated a higher prevalence in the multifocal group, but this trend did not reach statistical significance (9.2% vs 20%, $P = .07$). Parents' age, ethnic identity, highest level of education, and established diagnosis of depression did not differ significantly between the 2 groups, nor did the time since diagnosis or time since last treatment.

Retinoblastoma treatment features are summarized in Table 2. A comparison (unifocal vs multifocal retinoblastoma) revealed differences in use of systemic chemotherapy (29.5% vs 88.9%, $P < .001$), intra-arterial chemotherapy (65.4% vs 46%, $P = .02$), laser thermotherapy (17.9% vs 63.5%, $P < .001$), and cryotherapy (17.9% vs 52.4%, $P < .001$). In addition, there was a significant difference in the average number of different treatment modalities at the time of interview (2.1 unifocal vs 4.1 multifocal, $P < .001$). There were no significant differences between the 2 groups regarding treatment frequency with enucleation, intravitreal chemotherapy, external beam radiotherapy, or plaque radiotherapy.

• **PSYCHOLOGICAL FUNCTIONING:** Overall results from the psychological assessments for parental depression (BDI), parental anxiety (BAI), and parental stress (PSI 4-SF) are listed in Table 3. A comparison of scores between the unifocal and multifocal groups is included.

Overall, scores above the minimal level (mild, moderate, and severe are considered to be clinically relevant) were found for depression in 26.7% of parents (mild 16.8%, moderate 4.6%, severe 5.3%) and for anxiety in 35.8% (mild 21.2%, moderate 8.0%, severe 6.6%). The PSI 4-SF Total Stress Scores (TSS), as well as the scores in each domain including PD, Parent-Child Dysfunctional Interaction (P-CDI), and Difficult Child (DC), revealed scores considered to be on average, within the normal range (<85th percentile).

Higher BDI scores reflective of severe depression were found in more parents of patients with multifocal disease as compared to unifocal (1.4% vs 10.2%, $P < .02$). Assessment results that did not differ between the 2 groups included less severe depression (minimal, mild, and moderate), anxiety (minimal, mild, moderate, and severe), and stress (PD, P-CDI, DC, TSS).

• **KNOWLEDGE ASSESSMENT:** Results of the knowledge assessment survey are reported in Table 4. A comparison (unifocal vs multifocal retinoblastoma) revealed differences in knowledge assessment. Parents of patients with multifocal disease demonstrated a poorer understanding of unilateral heritability (correct answer: 56.2% vs 35.0%, $P = .01$), risk for second malignant neoplasms in patients with heritable retinoblastoma (correct answer: 82.2% vs 66.7%, $P = .04$), and risk for second malignant neoplasms in patients with sporadic retinoblastoma (correct answer 37.0% vs 20.0%, $P = .03$). The overall mean knowledge score for the entire group was 70.2% and did not differ between the 2 groups. Further, understanding of the metastatic potential of retinoblastoma, treatment options, heritability of bilateral retinoblastoma, and the 2 types of retinoblastoma (sporadic and germline) did not differ in the 2 groups, with total scores ranging from 68.4% to 97.2% correct. Scores pertaining specifically to questions on the heritability of bilateral retinoblastoma

and the risk of secondary malignancies were poor (mean <80%, range 20.0%–82.2%).

• **ANALYSIS OF RISK FACTORS FOR DEPRESSION AND ANXIETY IN PARENTS OF PATIENTS WITH RETINOBLASTOMA:** Results of the BDI and BAI per parent/guardian and affected child are reported in Tables 5 and 6, respectively. For purposes of analysis of contributing factors for depression and anxiety, the minimal and mild groups (M/M) were combined, as were the moderate and severe groups (M/S). This was done to reflect the high clinical relevance of a BDI score, indicating moderate or severe depression, or a BAI score of moderate or severe anxiety; moderate and severe scores should prompt timely psychological evaluation.

Analysis of factors related to M/S depression revealed significant correlation with previous diagnostic reports of parental depression (30.0% vs 3.9%, $P < .001$) (Table 5). Other parent features, including "relationship to the child," "marital status," and "parent highest level of education," did not result in statistical correlation on the BDI survey. Other affected child features, including "child developmental delay," "family history of retinoblastoma," "child genetic testing," "interval diagnosis to interview," "time since last treatment," and "treatment history," revealed no statistically significant correlation with degree of depression.

Analysis of factors related to M/S anxiety revealed significant correlation with previous report of parental history of depression (33.3% vs 8.6%, $P < .001$), parent highest level of education at high school or less vs college or beyond (29.2% vs 10.9%, $P = .031$), and parental report of "child developmental delay" (31.5% vs 11.3%, $P = .019$) (Table 6). Other parent features of "relationship to the child" and "marital status" did not achieve statistical correlation on the BAI, nor did affected child features of "child developmental delay," "family history of retinoblastoma," "child genetic testing," "time since diagnosis," "time since last treatment," or "treatment history."

• **ANALYSIS OF RISK FACTORS FOR PARENTING STRESS IN PARENTS OF PATIENTS WITH RETINOBLASTOMA:** Statistical analysis of Parent and Affected Child characteristics and their relationship to scores on the PSI 4-SF in our parent population is listed in Table 7. These were analyzed for the TSS and for the individual domains of PD, P-CDI, and DC. Although all stress scores fell within the normal range (<85th percentile), there were statistically significant correlations between several parent and child characteristics. Parental relationship to the child revealed that mothers (vs other) scored higher (greater stress) on the PD domain ($P = .001$), and previous report of diagnosis of depression scored higher in each domain: PD ($P = .001$), P-CDI ($P = .009$), DC ($P = .025$), and TSS ($P = .001$). Regarding affected child, parents reporting a diagnosis of "child developmental delay" scored higher on P-CDI ($P < .001$), DC ($P = .007$), and TSS ($P = .001$). Parents who were more than 6 months from their child's initial retinoblastoma diagnosis scored higher on the P-CDI ($P = .005$), DC ($P = .001$), and TSS ($P = .05$), and those more than 6 months from their child's last treatment scored higher on DC ($P = .011$). Parent features of "marital status" and "highest level of education" did not achieve statistical significance on the PSI 4-SF survey of these parents, nor did the child features of "family history of retinoblastoma" and "child genetic testing" reach significance.

DISCUSSION

FEW STUDIES HAVE FOCUSED ON THE LONG-TERM PSYCHOlogical functioning of retinoblastoma survivors, and most of these have, perhaps surprisingly, revealed that retinoblastoma survivors have an overall good quality of life.[25–28] There is some evidence that retinoblastoma survivors have lower educational attainment and may have impairment in activities of daily living at greater rates than their unaffected sibling counterparts.[26,28–31] Further study on the reproductive behavior of retinoblastoma survivors has shown that the perceived risk of a retinoblastoma survivor having a child with retinoblastoma influences their reproductive behavior.[32]

The most comprehensive study on the psychological functioning of retinoblastoma survivors, that of 470 adults, revealed an optimistic outlook for these patients.[27] Survivors reported lower levels of depression, anxiety, and somatic symptoms than had been previously reported for other nonretinoblastoma cancer survivors.[33,34] Further, a study by Ford and associates[27] was the first to show that unilateral and bilateral retinoblastoma survivors did not differ in the frequency of diagnosed depression, anxiety, or other psychiatric conditions. These results suggest that adult survivors of retinoblastoma cope and function well, even in the setting of chronic health problems and greater health-related fears.

• **PARENTAL PSYCHOLOGICAL FUNCTIONING IN CHILDHOOD DISEASE:** Prior work has established that parents of children with chronic illnesses, including juvenile arthritis, diabetes, and cystic fibrosis, suffer from higher levels of parental stress.[35,36] This increased stress level can impact the child-parent relationship and affect compliance with treatment and maintenance of the childhood illness, particularly when parents must participate in the treatment.[35] Parental stress in pediatric cancer and the effect of a pediatric cancer diagnosis on the family has also been studied,[37–42] but the field of psych-oncology and parental stress is not well developed.

Even less is known about the impact of serious pediatric ophthalmic conditions on parental depression, anxiety, and stress levels. There are few studies that address the issue of pediatric ophthalmic conditions on the psychological health of the child, the parents, and the family unit.

Parental stress was measured in 2 studies of children with congenital cataract.[43,44] In the first study, the total parent stress scales were within the normal range, but the authors confirmed their hypothesis that parents of children with aphakia would have higher stress levels owing to the burden of contact lens wear and visual rehabilitation.[44] Recommendations from this study included consideration of treatment modalities to reduce parental stress, monitoring of parent stress, and collaboration between ophthalmologists and mental health professionals to provide support to these parents.[43] In the second study, parenting stress levels in infants with cataract was studied in the Infant Aphakia Treatment Study.[44] The TSS at 3 months was higher in the group receiving an intraocular lens compared to those left aphakic.[44] This disproved the authors' theory that parents of the aphakic children would have higher stress levels. The authors postulated that the increased parental stress levels in the intraocular lens group was attributable to a greater number of complications following surgery, including an increasing number of intraocular surgeries. This conclusion was reinforced by the resolution of this difference in stress levels at 4.25 years postsurgery.

Further study on parental psychological health with infants with glaucoma has been investigated. Dada and associates[45] administered a patient health questionnaire to parents of children with congenital glaucoma and found a high prevalence of parental depression (22% with moderate depression and 11% with severe depression). This led them to recommend that ophthalmologists who care for patients with congenital glaucoma offer psychological counseling to parents of these patients.[45]

• **PARENTAL PSYCHOLOGICAL FUNCTIONING IN RETINOBLASTOMA:** Parental psychological functioning in retinoblastoma has not been well studied, and only a few qualitative reports suggested higher levels of stress in parents of patients recently diagnosed with retinoblastoma, especially in those requiring enucleation.[46,47] A recent longitudinal assessment of parental stress in patients with retinoblastoma revealed no evidence of increased parental stress levels, either shortly after the child was diagnosed or at age 5 years.[48] This was contrary to the authors' expectations. However, in 1 subdomain, there was a significant contribution of parental stress directed toward the child that appeared to contribute to reduced child functioning. These findings are consistent with other studies suggesting that parental stress influences child cognitive outcomes.[49,50] The studies reviewed above have repeatedly demonstrated that parental psychological functioning is impacted by childhood disease, both ophthalmic and systemic, and furthermore, poor parental functioning is associated with suboptimal child development.

• **CURRENT STUDY ON PARENTAL DEPRESSION, ANXIETY, AND STRESS IN RETINOBLASTOMA:** Our analysis is the first comprehensive assessment of psychological functioning of parents of newly diagnosed and treated patients with retinoblastoma. We specifically examined the level of parental depression, anxiety, and stress relative to the child manifesting unifocal (presumed somatic) vs multifocal (heritable) retinoblastoma. Our results disclosed a high percentage of parents who displayed mild, moderate, or severe depression on the BDI test (26.7%) and mild, moderate, or severe anxiety on the BAI test (35.8%). We grouped these scores together to be clinically meaningful, as any score indicating significant symptoms, may warrant follow-up and further evaluation. We further evaluated parental stress levels, and scores generally were within the normal range (44.6% [normal <85%]).

A recent U.S. population survey of depression revealed that 8.1% of Americans aged 20 years and older demonstrated depression based on scores from the Patient Health Questionnaire (PHQ9),[51] and another survey, the National Comorbidity Study Replication, showed 12-month prevalence of major depressive disorder at 6.7% (mild 19.5%, moderate 50.1%, and serious 30.4%).[52] Regarding anxiety, the National Comorbidity Study Replication revealed that an estimated 18.1% of U.S. adults had an anxiety disorder over a 12-month period from 2001 to 2002.[52] Our present data show that parents of children with retinoblastoma demonstrate more than 3-fold the national prevalence of depression (n = 37, 26.7%) and nearly 2-fold the prevalence of anxiety (n = 49, 35.8%). Our data regarding parental depression are similar to those found in a study on parental depressive symptoms in children with cancer or brain tumors compared to a control group of parents with healthy children (30.7% vs 6.4%, $P < .001$).[53] And although the tools used to measure depression and anxiety in these studies differ from our surveys, all assessment tools have been scientifically validated. Comparison to population norms is often limited by assessment tool variety, but still provides a useful benchmark.

In our analysis, the highest BDI scores, reflective of severe depression, were found more often in parents of patients with multifocal disease as compared with unifocal disease ($P = .026$). The nature of multifocal retinoblastoma with known hereditary factors and the knowledge of lifelong risk for secondary malignancy could have contributed to this rate of severe depression. There was no significant difference in the level of anxiety or stress between the 2 groups.

In our study, we sought to create an evaluation of the knowledge base of the parent regarding retinoblastoma by employing a standard questionnaire with 7 basic questions about the disease that most informed parents of children with retinoblastoma should be able to answer correctly (Table 4). This information allowed us to discover if parents were fully informed or if there was a knowledge gap. Additionally, we speculated that a higher knowledge level could potentially impact parental depression, anxiety, and stress, particularly in parents of children with multifocal

(germline) disease who would be at risk for hereditary and second malignancy concerns, whereas parents of unifocal retinoblastoma children typically carry no further life-threatening issues. The results of this knowledge assessment revealed that the most basic questions were answered correctly regarding topics of retinoblastoma potential for metastasis, retinoblastoma treatment options, and retinoblastoma types (questions 1, 2, and 5, with score 91.7%–97.0%). For the more in-depth questions on heritability of retinoblastoma (questions 3 and 4), it was apparent that overall understanding was fairly poor (46.6%–72.9%), with significantly poorer understanding of transmission rate for unilateral retinoblastoma in those parents of children with multifocal retinoblastoma. Additionally, there was fairly poor understanding of the risk for secondary malignant neoplasms (questions 6 and 7), with scores ranging from 29.3% to 75.2%, particularly in parents of children with multifocal retinoblastoma for second cancer type and for sporadic retinoblastoma risks. This relatively poor knowledge base in parents of children with multifocal retinoblastoma underscores the difficulty in understanding of this genetically regulated, multifaceted malignancy.

Analysis of parent and patient demographics revealed an interesting finding: that parent-reported developmental delay in their affected child showed a trend to be more common in patients with multifocal disease (Table 1). This trend may be expected owing to the effect of cytogenetic deletions involving the 13q14 region that can result in deletions of additional regional genes that could cause developmental delay.[54] Other parent and patient demographics and treatment patterns also revealed expected statistics that more mothers enrolled in the study than "other" (72.8% mothers vs 25.0% fathers vs 2.2% legal guardians) and that the multifocal group demonstrated higher likelihood of a positive family history (3.8% vs 31.3%, $P = .001$), younger age at diagnosis (9.2 months vs 20.5 months, $P < .001$), and genetic testing revealing germline mutation (24.0% vs 72.1%, $P < .001$). Treatment differences between the unifocal and multifocal groups revealed trends that are typical for our practice. Of importance for analysis of psychological functioning was that there exists no difference between the 2 groups in the rate of enucleation (23.1% vs 20.6%). Statistically significant differences in mean number of treatments in the 2 groups at the time of interview (2.1 vs 4.1, $P < .001$) could have contributed to parental psychological functioning.

We further explored clinical factors that could be related to parental depression or anxiety in Tables 5 and 6, respectively. For analysis and as noted above, we used results of the BDI and BAI scores and combined groups (M/M and M/S) to reflect a category of high clinical relevance for depression or anxiety that might prompt the ocular oncologist to suggest psychological intervention, whereas those in the lower ranges might not require as immediate attention. For parental depression analysis, parents reporting a previous diagnosis of depression were more likely to score in the M/S range on the BDI ($P < .001$). This further reinforces that in our patient population, the BDI was accurate in screening for depression. For parental anxiety analysis, there were several factors of importance. Greater anxiety (M/S) was detected in parents with history of depression ($P < .001$), education to a level of high school or less ($P = .031$), and parent with child demonstrating developmental delay ($P = .019$). This is consistent with the well-established findings of increased anxiety and stress in parents of patients with developmental and cognitive delay.[49,55–58]

Further analysis into clinically relevant parental depression and anxiety revealed that even those with no history of previous depression were at risk for moderate-to-severe depression (3.9%) and moderate-to-severe anxiety (8.6%), based on the BDI and BAI. These statistics represent a group of clinically depressed or anxious parents who have not been previously identified as depressed or anxious, and should prompt the ocular oncologist or ophthalmologist to help not only the child, but also the parent. Further, this parental depression and anxiety could potentially impact the relationship and development of the affected child.

Measurements of parental stress, parental distress, parent-child dysfunctional interaction, and difficult child scores were analyzed in depth and found generally to be within the normal limits. However, there were a few important findings in which certain factors prompted higher stress levels. By comparative analysis, we identified potential factors for increased parental stress such as parental distress in mother (vs other) ($P = .001$) and several levels of stress in those with history of depression ($P = .025$ to $P = .001$), those with child developmental delay ($P = .001$ to $P < .001$), and those with greater interval from diagnosis to interview ($P = .005$ to $P = .001$) (Table 7). However, the overall finding of stress levels within the normal level for parents is consistent with a previous study of parents of patients with retinoblastoma[48] but is in contrast with studies in other pediatric cancers that show overall higher levels of parental stress.[40–42,49,59]

Prior to this study, our ocular oncology practice did not routinely screen for poor psychological functioning in parents of patients undergoing treatment for retinoblastoma. Of course, if it were evident to our physicians that a parent was suffering from depression or anxiety, we would suggest psychological evaluation and, if the parent gave permission, contact their primary care physician to alert and engage them. The results of this study demonstrate that a more proactive approach on the part of the multidisciplinary team caring for patients and families with retinoblastoma is likely required to identify all individuals who are experiencing clinically relevant levels of depression and/or anxiety.

There are limitations to this analysis. Our study was a comparison of unifocal vs multifocal retinoblastoma as a surrogate for somatic vs germline mutation retinoblastoma, as not all patients had genetic testing results at first visit and some declined genetic analysis (overall 19.9% declined

genetic testing). Once genetic testing was realized, this could have influenced the psychological status of the families. Further, the interviews were taken at random time interval from establishment of the diagnosis, which could impact parents' psychological function and knowledge. Future study with larger numbers of patients and longer follow up will address the longitudinal evaluation of parent psychological functioning to better evaluate the effect of variables including time since diagnosis, number of treatments required, and others. Additionally, we invited only 1 parent to take the survey, and typically the mother volunteered (73%), but parent sex could have influenced results. Lastly, there are numerous additional clinical factors that could have impacted the parent psychological status, such as tumor classification (size), type of treatment, tumor response to therapy, episodes of tumor recurrence, child's visual potential, and many others. These confounding factors could influence parental psychological functioning and the results on the surveys. We anticipate future investigations might include some of these variables.

In summary, we demonstrated that most parents of children with retinoblastoma fortunately display minimal depression, minimal anxiety, and normal stress scores. However, there were significant numbers of parents with moderate-to-severe depression, moderate-to-severe anxiety, and higher stress scores, particularly those whose children have multifocal disease. Factors that promote poorer psychological function include previous history of parental depression and knowledge that their affected child has developmental delay. Poor parental psychological functioning can impact interaction with the child and lead to parent-child dysfunction. The potential impact of these psychological findings on the family unit and the ultimate child outcome is not clearly understood and should be further explored. Physicians caring for patients with retinoblastoma should consider methods to identify parents who may be suffering from depression, anxiety, or stress and refer for psychological counseling when necessary. Based on the results of this study, and the relatively high percentage of parents with worrisome psychological functioning, we plan to work with our colleagues in primary care, psychiatry, and psychology to develop a screening and intervention program in our practice. This is an important feature of the clinical relevance of this study.

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