

Risk of Ocular Pathology in Rett Syndrome

Ashvin Babu, BS; Faruk H. Orge, MD

ABSTRACT

Purpose: To assess the risk of developing ocular alignment disorders, refractive errors, amblyopia, and nystagmus in patients with Rett syndrome.

Methods: This retrospective cohort study used de-identified patient data from the TriNetX US Collaborative network and compared a Rett syndrome and a control cohort. Propensity score matching was conducted to balance demographics and well-characterized comorbidities. Statistical analysis calculated risk ratios (RRs) and 95% confidence intervals (CIs), with significance defined by excluding CIs between 0.9 and 1.1.

Results: Patients with Rett syndrome had an increased risk of developing strabismus (RR: 3.39; CI: 2.47 to 4.65) and risk for the specific horizontal subtypes of esotropia (RR: 4.06; CI: 2.26 to 7.26) and exotropia (RR: 2.92; CI: 1.83 to 4.68). Additionally, patients with Rett syndrome had an increased risk of developing amblyopia (RR: 1.90; CI: 1.28 to 2.82) and nystagmus (RR: 1.98; CI: 1.12 to 3.53). No differences in risk were found for astigmatism, myopia, and hyperopia development given Rett syndrome diagnosis.

Conclusions: These findings demonstrate the importance of regularly monitoring ocular health in patients with Rett syndrome and a need for further investigation into the underlying mechanisms linking the disease with these specific ocular pathologies.

INTRODUCTION

Rett syndrome, a disorder characterized by a pathological variant in the Methyl-CpG-binding protein 2 (MECP2) on the X chromosome, leads to widespread neurodevelopmental dysregulation, primarily in females. Although these patients may initially follow typical early development during their first 6 to 18 months, they soon experience a regression of cognitive, motor, and communication processes. This regression presents with wide-ranging clinical manifestations from respiratory irregularities and seizures to autonomic dysfunction.^{1,2} Due to systemic dysregulation of the central nervous system, neurological and motor deficits ensue, including impaired synaptic plasticity, neurotransmitter imbalances, and disrupted neuronal maturation. Additionally, Rett syndrome can lead to underdevelopment in the corticospinal tracts, basal ganglia circuits, and cerebellar pathways, which are essential for normal motor coordination and control.^{2,3}

Although existing literature has focused on the disease's neurological and motor consequences, ocular pathologies are significant, unexplored aspects of the disorder.^{2,3} A prior study demonstrated MECP2 protein expression in various ocular tissues, including the retina, cornea, and optic nerve. The study suggests a significant role of MECP2 in ocular development and function.⁴ There has been limited analysis of the degree of ocular involvement in Rett syndrome, which may provide further insights into the broader ocular disruptions caused by

From the Departments of Ophthalmology and Pediatrics, University Hospitals Cleveland Medical Center, and Case Western Reserve University School of Medicine, Cleveland, Ohio.

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Address correspondence to Ashvin Babu, BS, 1750 Ansel Road, Cleveland, OH 44106; email: axb1045@case.edu.

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TABLE 1	
ICD-10 Code List	
Condition	ICD-10 code
Autism	F84.0
Cerebral palsy	G80
Down syndrome	Q90
Cerebral infarction	I63
Retinopathy of prematurity	H53.1
Family history of eye disorders	Z83.51
Esotropia	H50.0
Exotropia	H50.1
Strabismus (all forms)	H50
Astigmatism	H61.1
Amblyopia	H53.0
Nystagmus	H55.0
Myopia	H52.1
Hyperopia	H52.0
Hordeolum	H00.019
Rett syndrome	F84.2
Condition	CPT code
Ophthalmology services/procedures	1012793

it. Current studies analyzing prevalence are limited by small sample sizes that fail to provide accurate representations of the Rett syndrome population. This study addresses these current gaps by accessing a larger patient cohort. The study explored the risk of developing ocular alignment disorders, refractive-related disorders, amblyopia, and nystagmus in patients with Rett syndrome through the TriNetX US Collaborative platform. Understanding these associations will offer a more comprehensive view of Rett syndrome and may guide clinicians toward improved, holistic approaches that address the ocular complications of the disease.

PATIENTS AND METHODS

This retrospective cohort study used data from the TriNetX US Collaborative network, which includes more 110 million de-identified patient records from 66 health care organizations across the United States. Because the data were de-identified in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule (§164.514(a)), no informed consent was required. De-identification was verified by a qualified expert

as defined in HIPAA's §164.514(b)(1) (December 2020). Data collection occurred in August 2024.

The study evaluated the association between Rett syndrome and common ocular pathologies. A cohort of patients with a diagnosis of Rett syndrome was compared to a control group with a diagnosis of a hordeolum. Diagnosis of hordeolum was selected as the control cohort due to its limited associations with the specific ocular pathologies analyzed in the study but also its ability to be more likely diagnosed as having ocular conditions. Patients with Rett syndrome were identified by their ICD-10 codes, excluding males, whereas the control group excluded patients with Rett syndrome and males. Males were excluded from the study due to their significantly lower prevalence and severe clinical presentations that most often lead to death compared to the milder clinical presentation in females.

To ensure comparability between the cohorts, propensity score matching was conducted using TriNetX's analytic tool. A 1:1 greedy matching algorithm with a 0.25 caliper was applied. Matching criteria included demographic factors such as age, race, and ethnicity. Additional matching was performed for comorbidities and potential risk factors for ocular pathology. Covariate balance was assessed using standardized differences, with a threshold of 0.10 indicating imbalance. ICD-10 codes for the matching criteria are listed in **Table 1**.

The study's outcomes of interest included esotropia, exotropia, strabismus (all types), astigmatism, amblyopia, nystagmus, myopia, and hyperopia, identified through their corresponding ICD-10 codes (**Table 1**). Vertical strabismus could not be individually accessed due to a lack of patients with concurrent Rett syndrome and hordeolum after matching. Outcomes that occurred before diagnosis were excluded from analysis.

Statistical analysis was performed on the TriNetX platform. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated, with significance determined by excluding CIs between 0.9 and 1.1, which were deemed non-significant.

RESULTS

Following propensity score matching, there were 3,230 patients in the Rett syndrome and control cohorts. Cohorts were broadly categorized as either an alignment disorder, refractive disorder, amblyopia, or nystagmus. All values were successfully

TABLE 2

Propensity Score Matching Results Between Rett Syndrome and Control Cohort

Characteristic	Before matching			After matching		
	Rett syndrome (n = 3,516)	Control (n = 132,976)	SMD	Rett syndrome (n = 3,230)	Control (n = 3,230)	SMD
Demographics, mean $\pm$ SD						
Current age (y)	23.2 $\pm$ 14.3	43.5 $\pm$ 23.6	1.039	23.4 $\pm$ 14.4	23.3 $\pm$ 14.2	0.001
Index age (y)	14.7 $\pm$ 13.7	34.2 $\pm$ 24.1	0.990	14.9 $\pm$ 13.8	14.9 $\pm$ 13.6	0.009
Race/ethnicity ^a						
White	64.10%	59.90%	0.087	64.10%	64.70%	0.013
American Indian or Alaska Native	0.50%	0.50%	0.004	0.50%	0.30%	0.024
Unknown race	14.30%	10.00%	0.130	14.10%	14.40%	0.008
Native Hawaiian or Other Pacific Islander	0.60%	1.10%	0.062	0.60%	0.40%	0.026
Unknown ethnicity	24.00%	21.00%	0.073	23.90%	23.50%	0.009
Not Hispanic or Latino	63.00%	64.50%	0.033	62.90%	63.70%	0.017
Hispanic or Latino	13.00%	14.50%	0.042	13.20%	12.80%	0.012
Black or African American	9.10%	17.60%	0.252	9.20%	8.80%	0.015
Other race	6.30%	5.90%	0.018	6.30%	6.30%	0.001
Asian	5.20%	5.00%	0.007	5.20%	5.10%	0.004
Diagnoses						
Autism	8.90%	0.30%	0.442	7.60%	7.10%	0.018
Cerebral palsy	6.90%	0.20%	0.363	6.10%	6.10%	< 0.001
Down syndrome	0.30%	0.20%	0.024	0.30%	0.30%	< 0.001
Cerebral infarction	0.40%	1.20%	0.094	0.40%	0.50%	0.019
ROP	0.30%	0.10%	0.034	0.30%	0.30%	< 0.001
Family history	0.30%	0.30%	0.008	0.30%	0.30%	< 0.001
Ophthalmology services/procedures	5.00%	12.00%	0.225	4.80%	4.50%	0.016

Abbreviations: ROP, retinopathy of prematurity; SD, standard deviation; SMD, standardized mean difference.

^a Race and ethnicity were determined based on presence of these designations within the electronic health record.

matched with a standard mean difference below 0.1 (Table 2).

Alignment Disorder

The relative risk of developing strabismus, in any form, given Rett syndrome diagnosis was significantly increased compared to the control group with a RR of 3.39 (CI: 2.47 to 4.65). When examining specific types of strabismus, exotropia and esotropia each demonstrated significantly increased risks of 2.92 (CI: 1.83 to 4.68) and 4.06 (CI: 2.26 to 7.26), respectively (Figure 1).

Refractive Disorder

Refractive errors did not show increased associations with Rett syndrome. Astigmatism, hyperopia, and myopia did not meet the threshold of significant with RRs of 0.90 (CI: 0.72 to 1.12), 0.79 (CI: 0.60 to 1.05) and 0.86 (CI: 0.67 to 1.10), respectively (Figure 1).

Amblyopia

Patients with Rett syndrome had a significantly increased risk of developing amblyopia with a relative risk of 1.90 (CI: 1.28 to 2.82) (Figure 1).

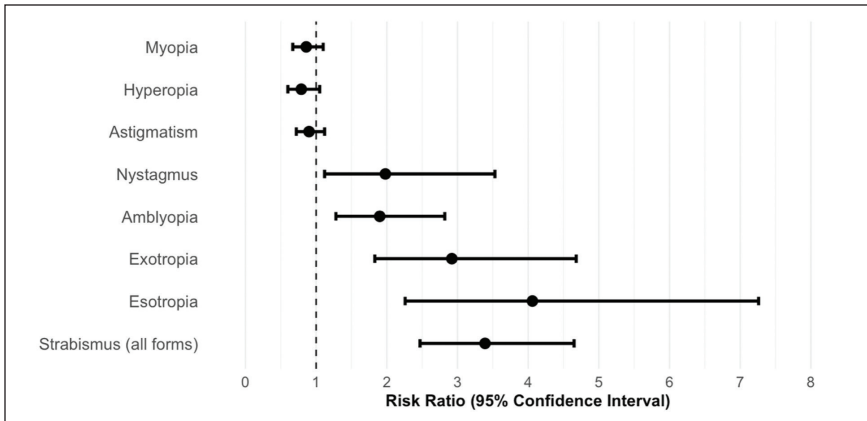


Figure 1. Forest plot of the risk ratio interval of nystagmus, amblyopia, myopia, hyperopia, astigmatism, esotropia, exotropia, and all subtypes of strabismus. The plot includes 95% confidence intervals for each condition.

Nystagmus

Patients with Rett syndrome had a significantly increased risk of developing nystagmus with a relative risk of 1.98 (CI: 1.12 to 3.53) (**Figure 1**).

DISCUSSION

Our study suggests that patients with Rett syndrome have an increased risk of developing strabismus, amblyopia, and nystagmus. Patients with Rett syndrome do not have an increased risk of developing astigmatism, myopia, and hyperopia. Strabismus is defined by ocular misalignment due to impaired extraocular muscle coordination. Although the exact pathophysiology behind this development has not been fully elucidated, strabismus has been linked to various developmental conditions, including Down syndrome, cerebral palsy, and retinopathy of prematurity. Our study demonstrated that patients with Rett syndrome are more than three times more likely to develop strabismus. Notably, our research found increased risks for both horizontal subtypes of strabismus: esotropia and exotropia. These significantly elevated risks align with prior studies that have cited strabismus prevalence among patients with Rett syndrome, albeit with limited sample sizes. One case series cited 2 of 7 patients with Rett syndrome having strabismus, another reported 1 of 11 patients, and a study analyzing videos cited 9 of 22 patients with Rett syndrome.⁵ Although these broadly ranging values are greater than the 1% to 2% risk in the general population, current studies have lacked the standardization and focus on ocular manifestations offered in our analysis. Our findings emphasize the importance of monitoring ocular alignment in patients with Rett syndrome, especially because many patients often become de-

pendent on eye movement as a primary means of communication.^{6,7}

Patients with Rett syndrome were not at increased risk of refractive errors. Although astigmatism is likely induced by corneal structure, the exact mechanism behind its occurrence would be difficult to ascertain through the current study methods.⁸ Prior studies have shown an increased risk of refractive errors in Rett syndrome does not support our observations of no association of increased risk of refractive errors in patients with Rett syndrome.^{9,10} Our study found no difference in risk for myopia and hyperopia. These results may suggest patients with Rett syndrome are at a lower risk for developing refractive errors compared to developing the other ocular manifestations discussed.

Our study showed increased risks of developing both amblyopia and nystagmus given a diagnosis of Rett syndrome. Amblyopia is a neurodevelopmental eye disorder with impaired ocular-brain signaling leading to the perceived lazy eye, whereas nystagmus is an ocular pathology characterized by rapid, repetitive, rhythmic eye movements. In our study, we found that patients with Rett syndrome had an almost two times increased risk of developing amblyopia and nystagmus. The increased risk of amblyopia may be attributed to the higher incidence of strabismus, which is also a risk factor for amblyopia.¹¹ The neurological impairments characteristic of Rett syndrome, particularly those affecting motor control and visual processing pathways, may also contribute to the development of both amblyopia and nystagmus.

CONCLUSION

Our study adds important insights into the specific ocular manifestations of Rett syndrome poorly

characterized in current literature, particularly the increased risks of strabismus, amblyopia, and nystagmus. However, this study is not without limitations. The analysis required reliance on ICD-10 coding, which can have inconsistencies in diagnosis due to variations in coding across different facilities and practices. This study was also unable to determine specific time intervals between Rett syndrome diagnosis and subsequent ocular disorder diagnosis. Due to the exploratory nature of our study, future studies may perform an investigation into the neurodevelopmental and genetic abnormalities that predispose patients with Rett syndrome to ocular misalignment, astigmatism, amblyopia, and nystagmus. Longitudinal studies also could provide further insight into the severity and onset of ocular pathology in patients with Rett syndrome.

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