

OCULAR FINDINGS IN RETT SYNDROME

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Abstract

Rett syndrome is a rare neurodegenerative disease, characterized by a year of normal development, followed by rapid mental and physical deterioration. A review of the medical literature reveals only limited research on ocular abnormalities in this population. The purpose of this paper is to investigate visual findings in a cohort of patients with Rett syndrome. Seven females with Rett syndrome ages 9 to 21 years (mean=14.7 years) were evaluated with portable equipment in residential care facilities, as a retrospective observational case series. The transilluminator-assisted assessment included examination of the external structures, pupillary response, cycloplegic retinoscopy, direct ophthalmoscopy, cover tests and visual tracking. Refraction revealed three had astigmatism in the potentially amblyogenic range, and two had significant spherical refractive errors. Two patients had strabismus, one with esotropia and another with exotropia. While the optic nerves appeared normal in all seven subjects, a majority demonstrated a

significant deficit in visual tracking skills. Only two subjects showed even minimal tracking ability. The current emphasis is on treatment to maximize the potential of individuals with disabilities. Visual therapy is viewed as appropriate in treatable conditions despite the devastating neurological degeneration seen in these females.

Key Words

astigmatism, autism, cerebrotrophic hyperammonemia, eye, genetic disorders, Israel, neurodegenerative disease, refractive error, Rett syndrome, vision, visual tracking

INTRODUCTION

Rett syndrome (cerebrotrophic hyperammonemia) (OMIM #312750^a) [see Appendix] is a rare neurodegenerative disease occurring exclusively in girls. It is considered as a pervasive developmental delay. The incidence is approximately one in 10,000 live births,¹ and it is responsible for at least 10% of females with profound developmental disability. This makes it the second most common cause of mental retardation in females in certain parts of the world, such as Sweden.²

Rett syndrome has a very consistent pattern. Developmental milestones appear normal until six to 18 months of age, when symptoms of autism, ataxia, and dementia emerge.^{3,4} Regression includes the loss of purposeful hand movements, slowing of head growth, seizures, breathing irregularities, teeth grinding and scoliosis. Deceleration in the rate of linear growth typically follows the first birthday.⁵ At about a year of age, an initial period of regression is apparent, followed by a period

of stabilization. Barring illness or other complications, survival into the fourth decade of life is expected, and patients have been reported as old as 77 years of age.⁶ In 1999 the discovery of mutations in the gene methyl CpG binding protein-2^b (MECP2), located on the X chromosome at the position Xq28, was found to be the cause of Rett syndrome.⁷ (See Appendix) Most males born with this mutation die shortly after birth, since they do not have an accompanying normal X chromosome to balance out the deleterious effects.⁸ Girls with Rett syndrome display many autistic features, such as loss of communication and social skills, poor eye contact, and lack of interest.⁵ Disappearance of the autistic-like features and emergence of markedly improved interaction and socialization occurs at about six to eight years of age. Eye contact resumes to a variable degree, and the ability to attend to a specific stimulus among varying stimuli can be developed. Rett syndrome is considered by many to be an autism spectrum disorder.⁹ Knowing the genetic origins of Rett's has enabled testing for early diagnosis and prenatal detection. Furthermore, researchers are investigating therapeutic intervention, both for improving the quality of life and for elongating the lifespan for this patient group. Recent evidence also points to the exciting possibility of reversing the negative consequences of Rett syndrome through genetic engineering.^{10,11} Few researchers have examined ocular abnormalities in Rett syndrome.¹² In 1995 von Tetzchner et al found that the visual function of 42 Rett patients aged 2 1/2 to 47 years demonstrated arrested development and abnormal visual processing that further worsened with advancing age.¹³ Saunders et al found significant refractive

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errors in 11 patients with Rett syndrome between the ages of four and 24 years of age.¹⁴ The purpose of this paper is to further explore visual function in this group.

METHODS

Seven female patients, diagnosed with Rett syndrome, were from 9 to 21 years of age with a mean age of 14.7 years. They were examined with portable equipment in residential group facilities as a retrospective observational clinical case series report. None of the patients had corrective lenses.

The evaluation included the following components:

- collection of limited and sometimes incomplete demographic data (age and gender), medical history and medication status available from the institutions.
- evaluation of the external structures and the anterior segment of the eyes, using a combination of a transilluminator without magnification and an ophthalmoscope at 10 cm with a +10.00 lens in the ocular cell.
- evaluation of pupil responses using the transilluminator.
- examination of the lens, media, optic nerve head, macular area/posterior pole with direct ophthalmoscopy, determination of optic nerve head cupping and size.
- cover testing for ocular alignment, determined by prism bar, when possible, or by estimation.
- measurement of the convergence near point.
- visual tracking ability, first utilizing a Wolff Wand (1.8 cm diameter highly reflective metal ball on a wand) and then transilluminator.
- retinoscopy under cycloplegia (cyclopentolate 1%) and when deemed necessary, a second ophthalmoscopy through the dilated pupils.

We would also have liked to include a measurement of visual acuity and visual fields. These were not possible due to the lack of availability of necessary equipment and poor patient cooperation.

RESULTS

Results showing the incidence of ocular abnormalities are summarized in Table 1. Previous eye/vision examination records were not available. No abnormalities of the anterior segment or external features were noted. Pupillary responses did not show abnormalities. All subjects had

Table 1: Ocular Findings in Rett Syndrome

Patient	Age	OD sphere	OD cyl	Axis	OS sphere	OS cyl	Axis	Bin-ocular Status	Tracking
1	21	PL	-3.00	180	PL	-3.00	180	Ortho	No tracking
2	13	PL	PL	–	PL	PL	–	LET= 30	No tracking
3	9	+6.00	-2.00	170	+5.00	-1.50	180	Ortho	Minimal tracking
4	PL	PL	PL	–	PL	PL	–	Ortho	Foveal fixation only
5	14	-4.00	-2.00	180	-3.00	-3.00	180	LXT=20	Minimal tracking
6	13	PL	PL	–	PL	PL	–	Ortho	Foveal fixation only
7	12	-2.00	PL	–	PL	-2.00	–	Ortho	No tracking

Abbreviations: OD = Right Eye, OS = Left Eye, LET = Left Esotropia, LXT = Left Exotropia

equal, round pupils that were reactive to light and the near reflex. Lens and media views along with optic nerve head evaluations showed cup/disc ratios in the normal range (0.1-0.3) without pallor, papilledema or atrophy. The evaluation of the posterior pole and macular areas were similarly unremarkable.

Five of the seven girls showed absolutely no visual tracking ability, and the remaining two showed only a very minimal ability to visually track a moving target. The eye muscles, however, showed no apparent restrictions of movement.

The evaluation of ocular alignment demonstrated the majority of the subjects were orthophoric (5/7, 71%) while two (29%) had significant strabismic deviations. One measured esotropia and the other, exotropia.

The cycloplegic refractive data showed some deviation from expected values in a normal population. As shown in Table 1, three of the seven patients (49%) were emmetropic, three had astigmatism in the amblyopic range (2.00 to 3.00 diopters), one also had high hyperopia (+6.00) and another moderate myopia (-4.00). One subject revealed simple mild myopia.

DISCUSSION AND CONCLUSIONS

None of the seven patients with Rett syndrome had abnormalities of the ocular structures. Formal visual acuity was difficult to measure with accuracy. This is due to poor verbal ability and a documented lack of attention.¹² Five of the seven Rett syndrome patients had significant refractive or strabismic abnormalities that could have impacted their vision.

It is interesting to note that the two patients who had neither significant refractive er-

ror nor strabismus, were able to fixate an object, but were still not able to track the object. Additionally, the two subjects who exhibited minimal tracking ability measured astigmatism as well as abnormal spherical refractions.

These findings corroborate those of von Tetzchner et al¹³ and are also in agreement with those of Saunders et al.¹⁴ This study also corroborates previous findings that the optic nerves of Rett patients were normal. The present study also indicates poor visual tracking function. This is in contrast to previous conclusions that these patients have good afferent visual pathway function. These researchers concur with the conclusion that spectacle correction may still be of use to assist in activities of daily living, alertness, and sociability.

The absence of cognitive loss following initial regression provides strong support for employing therapies to maximize communication and to preserve motor abilities, including visual-motor function. We believe that Rett's may not be a progressive disorder and could respond to fundamental therapies aimed at improving function.

Special attention might be directed to the issue of improving visual tracking behavior in Rett patients as part of an extensive treatment effort. These patients often survive into adulthood.¹⁵ Knowledge of the wide spectrum of clinical presentation is imperative to prevent delayed diagnosis and intervention. Data concerning genotype-phenotype correlations, such as how specific deletions in the MECP2^b (see Appendix) gene correlate with physical findings, are allowing further delineation of the disease process.¹⁶ Furthermore, isolated case reports demonstrate that L-

Carnitine^c (see Appendix) may be a possible treatment for Rett syndrome, further extending and enhancing quality of life.¹⁷ Therefore, all attempts toward addressing treatable problems such as refractive errors, strabismus and amblyopia should be made. It is possible that if treated, the patients might have better visual attention, decreased dependence and hence better quality of life.

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- a. Online Mendelian Inheritance in Man ®: OMIM, is a comprehensive, authoritative compendium of human genes and genetic phenotypes. It was created in 1985 by a collaboration between the National Library of Medicine and the William H. Welch Medical Library at Johns Hopkins. In 1995, OMIM was developed for the World Wide Web by NCBI, the National Center for Biotechnology Information.
- b. The X-linked methyl-CpG-binding protein 2 gene (MECP2) encodes a protein that links DNA methylation to transcriptional repression mediated by histone deacetylases.
- c. L-Carnitine is a naturally occurring amino acid which plays a vital role in the metabolism of fat. L-carnitine transports long-chain fatty acids across the mitochondrial membrane to be metabolized. L-carnitine aids in the release of stored body fat (triglycerides) into the bloodstream for energy.

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