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CASE REPORT OF THE ROLE OF OPTICAL COHERENCE TOMOGRAPHY IN RECOMBINANT GROWTH HORMONE THERAPY

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Purpose: To report the correlation between recombinant growth hormone (rhGH) dosage and retinal nerve fiber layer (RNFL) thickness values measured by optical coherence tomography in a case of pseudotumor cerebri syndrome (PTCS) after rhGH.

Methods: An 11-year-old girl was receiving rhGH for panhypopituitarism. The patient developed PTCS, and her rhGH dose was adjusted using optical coherence tomography RNFL thickness measurements. The linear correlation coefficient (r) and coefficient of determination (r^2) were calculated to assess the relationship between RNFL thickness and rhGH dose.

Results: As the rhGH dosage was increased, the RNFL thickness values also increased, especially when acetazolamide was excluded because of its confounding effect. (r = 0.64) In separate subgroup analysis, a higher acetazolamide dosage strongly correlated with reduced RNFL thickness (r = 0.77).

Conclusion: Although PTCS is a rare complication after rhGH therapy, its detrimental effects cannot be ignored. In our case report, we used optical coherence tomography RNFL values in addition to clinical findings to carefully titrate the rhGH dosage to prevent a flare-up of PTCS. Despite the obvious need for larger studies, our case report shows the value of RNFL thickness measured by optical coherence tomography and the valuable additional data it provides to refine rhGH therapy as an adjunct noninvasive method in PTCS.

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Pseudotumor cerebri syndrome (PTCS) after recombinant human growth hormone (rhGH) therapy is a rare but an important complication.[1] Cessation of the therapy is often adequate for reversal of PTCS; however, this is complicated by the growth requirements of the patient.[1] To the best of our knowledge, we report the first case of the prevention of flare-up of PTCS by titrating the rhGH dose based on retinal nerve fiber layer (RNFL) thickness values obtained by optical coherence tomography (OCT).

Case Report

An 11-year-old girl with a history of panhypopituitarism had been followed-up by the pediatric endocrinology (PE) team at University Hospitals Cleveland Medical Center since birth. She was referred to pediatric ophthalmology due to intermittent occipital headaches. A full ophthalmic examination was unremarkable except for the dilated fundus examination, which revealed +2 optic disc edema (ODE) in both eyes (Figure 1). The results of OCT of the optic discs revealed increased RNFL thickness in both eyes (Figure 2).

Magnetic resonance imaging showed pituitary hypoplasia in 2007, and treatment with hydrocortisone, levothyroxine, and somatropin

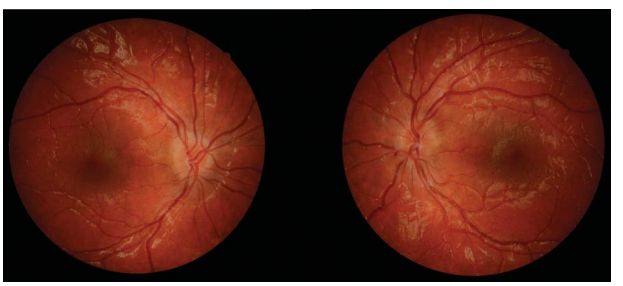

Fig. 1. Fundus photography of the patient at the first visit revealing bilateral ODEs.

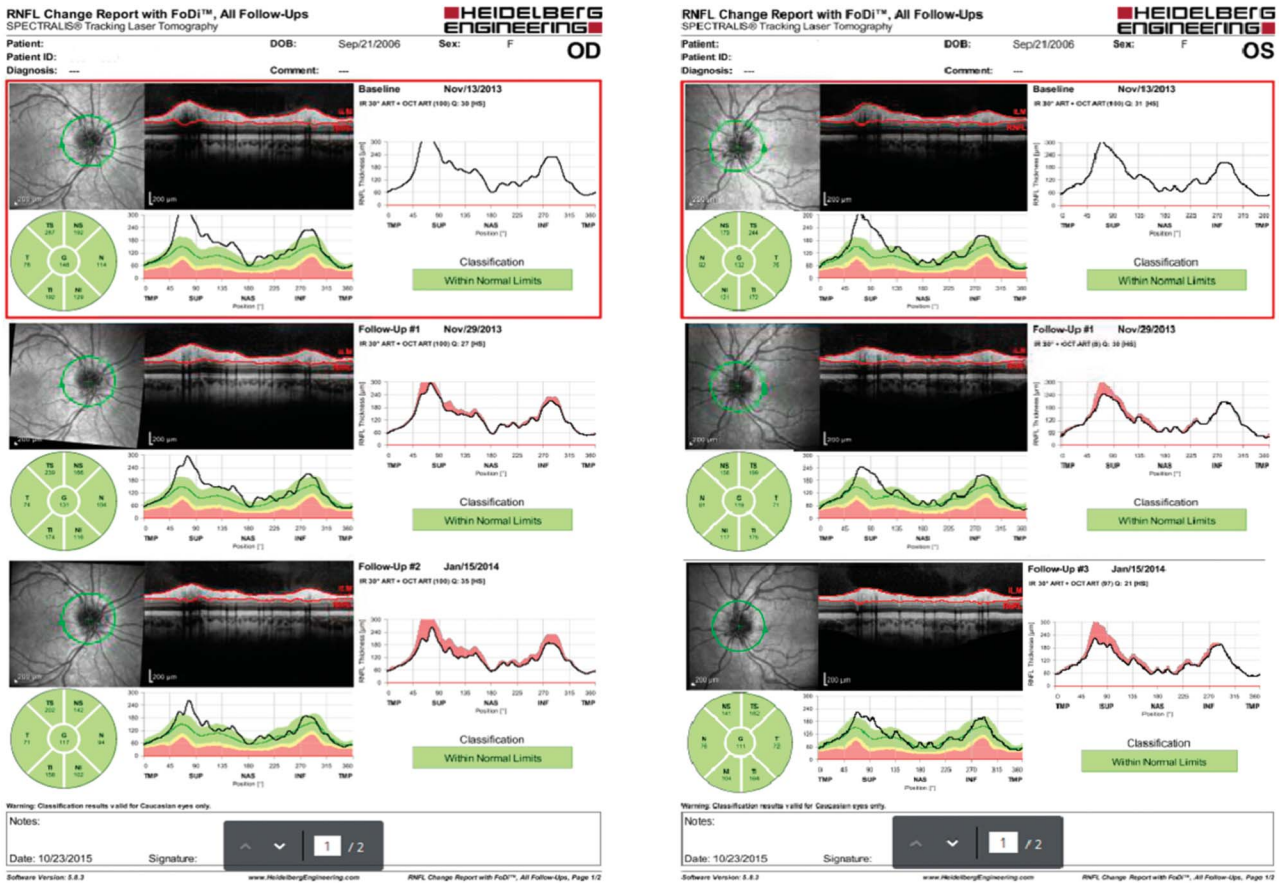

Fig. 2. Optical coherence tomography RNFL changes. On November 13, 2013, the patient was receiving a 0.8 mg/kg rhGH dose, and her OCT RNFL values were greatly increased. Fifteen days later, upon stopping rhGH therapy totally, the OCT RNFL values started decreasing, and after 2 months, the values returned to normal.

(rhGH) was started. Other examinations were otherwise normal. The patient was born at 39 weeks of gestation with a birth weight of 3,517 g. No apparent reason was found for her hypopituitarism.

Recombinant human growth hormone was stopped immediately, and magnetic resonance imaging and lumbar puncture were ordered to rule out PTCS. Visual acuity for both eyes was still 20/15, and ODE improved in the next follow-up after 2 weeks (Figure 2). Magnetic resonance imaging was negative, and lumbar puncture revealed high opening pressures, leading to confirmation of PTCS. Recombinant human growth hormone was started again, albeit on a lower dose at 0.3 mg/day reduced from 0.8 mg/day, and no ODE was noted in the next 2 months (Figure 2).

However, the patient's growth rate halted because of inefficient rhGH. After communication among the medical providers, the rhGH dose was increased from 0.3 mg/day to 0.5 mg/day. Three-month follow-up revealed mild ODE, which was confirmed with increased RNFL OCT values (Figure 3A). After consultations with the PE team, the rhGH dose was reduced to 0.3 mg/day again. Dilated fundus examination revealed improved ODE, which was confirmed with RNFL OCT values (Figure 3B). To increase the growth rate further, the PE team decided to increase the rhGH dose to 0.8 mg/day incrementally. Subsequent visits revealed normal optic discs and stable OCT values up to 0.7 mg/day. However, after 3 months on 0.7 mg/day, OCT RNFL values increased, and the dose was adjusted to 0.4 mg/day (Figure 3C). In addition to decreasing the dose of rhGH, 250 mg/day acetazolamide was started. At the 2-month follow-up, OCT RNFL values returned to baseline (Figure 3D). The PE team again began to incrementally increase the dose to 0.8 mg/day. Two months later, OCT RNFL values again increased above baseline despite the acetazolamide therapy (Figure 4A). A second lumbar puncture revealed high opening pressures. However, because of the slow growth rate, declining percentiles, and

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None of the authors has any financial/conflicting interests to disclose.

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(GH Dosage: 0.5 mg/day)

	OD	OS
Sup	196	179
Inf	146	140
Nas	112	85
Temp	74	74

A

(GH Dosage: 0.3 mg/day)

	OD	OS
Sup	175	157
Inf	133	133
Nas	104	81
Temp	72	75

B

(GH dosage: 0.7 mg/day)

OD	OS
213	208
138	142
110	85
72	81

C

(GH Dosage: 0.4 mg/day with 250 mg acetazolamide)

OD	OS
171	168
127	128
100	75
68	81

D

Fig. 3. A. OCT RNFL values with 0.5 mg/day rhGH. **B.** OCT RNFL values after decreasing the rhGH dose to 0.3 mg/dL. **C.** OCT RNFL values after increasing the rhGH dose to 0.7 mg/dL. **D.** OCT RNFL values after decreasing the rhGH dose to 0.4 mg/dL and starting 250 mg acetazolamide.

episodes of hypoglycemia, rhGH was not stopped completely but was instead reduced to 0.4 mg/day with 250 mg acetazolamide. Optical coherence tomography RNFL values were then the same as those at baseline (Figure 4B). As the PE team was not satisfied with the growth rate, the dose was increased to 0.8 mg/day. Clinical examination showed mildly elevated optic nerve head with elevated RNFL values (Figure 4C). We decided to increase the acetazolamide dose to 500 mg without changing the dose of rhGH. At her next visit, the patient had slightly lower RNFL values, but they had not returned to baseline (Figure 4D). Therefore, we decided to further increase the acetazolamide dose to 750 mg. At the next visit, the PE team reported that the patient's growth had reached a normal rate but requested to further increase the dose. Subsequent visits showed the RNFL values returning to baseline with 750 mg acetazolamide; therefore, the rhGH dosage was increased to 0.9 mg/day (Figure 5).

Methods and Results

The rhGH dose values were compared against the RNFL thickness values, and the Pearson's product moment correlation coefficient for sample statistic (r) and coefficient of determination (r^2) were calculated to assess the relationship using Microsoft Excel. (Microsoft, Redmond, WA) We performed three different analyses to explore the relationship between the RNFL and rhGH dosage in this single-patient case study. In the first analysis, we looked at the relationship between all RNFL values and rhGH dosage. The correlation between average RNFL values and its relationship with rhGH dosage were relatively weak ($r = 0.47$ and $r^2 = 0.22$) (Figure 6A). Calculating each quadrant separately also showed a relatively low correlation (Figure 6, B–E). In the second analysis, we removed the RNFL values under acetazolamide treatment and only compared nontreated RNFL values against the rhGH dosage. This time, the correlation for both the average values and quadrants separately was much higher ($r = 0.64$, $r^2 = 0.40$) (Figure 7). For the third analysis, we only calculated acetazolamide's effect on RNFL under 0.8 mg/mL rhGH, which revealed a high negative correlation. Higher doses of the drug correlated strongly with lower (i.e., thinner) RNFL values ($r = 0.77$, $r^2 = 0.59$) (Figure 8).

Discussion

In recent years, OCT has started to be used in neuro-ophthalmology practices, especially for the follow-up of ODE.[2] In a multicenter trial by the NORDIC Idiopathic Intracranial Hypertension Study Group, the OCT substudy committee showed

(GH Dosage: 0.8 mg/day with 250 mg acetazolamide)

	OD	OS
Sup	208	206
Inf	148	155
Nas	98	99
Temp	82	77

A

(GH Dosage: 0.4 mg/day with 250 mg acetazolamide)

	OD	OS
Sup	161	175
Inf	124	126
Nas	95	77
Temp	70	73

B

(GH Dosage: 0.8 mg/day with 250 mg acetazolamide)

OD	OS
197	225
145	135
111	97
75	80

C

(GH Dosage: 0.8 mg/day with 500 mg acetazolamide)

OD	OS
190	198
136	134
103	82
71	82

D

Fig. 4. A. OCT RNFL values after rhGH was increased to 0.8 mg/dL with 250 mg acetazolamide. **B.** OCT RNFL values after rhGH was reduced to 0.4 mg/dL with 250 mg acetazolamide. **C.** OCT RNFL values after increasing the rhGH dose to 0.8 mg/dL. **D.** OCT RNFL values after increasing acetazolamide to 500 mg.

(GH Dosage: 0.9 mg/day with 750 mg acetazolamide)

	OD	OS
Sup	153	163
Inf	121	124
Nas	89	79
Temp	68	73

Fig. 5. OCT RNFL values after increasing acetazolamide to 750 mg.

that idiopathic intracranial hypertension therapy with acetazolamide and weight loss effectively improved RNFL thickness values.[3] In part II of the study, the OCT measurements were shown to strongly correlate with the Frisen grading of papilledema.[4]

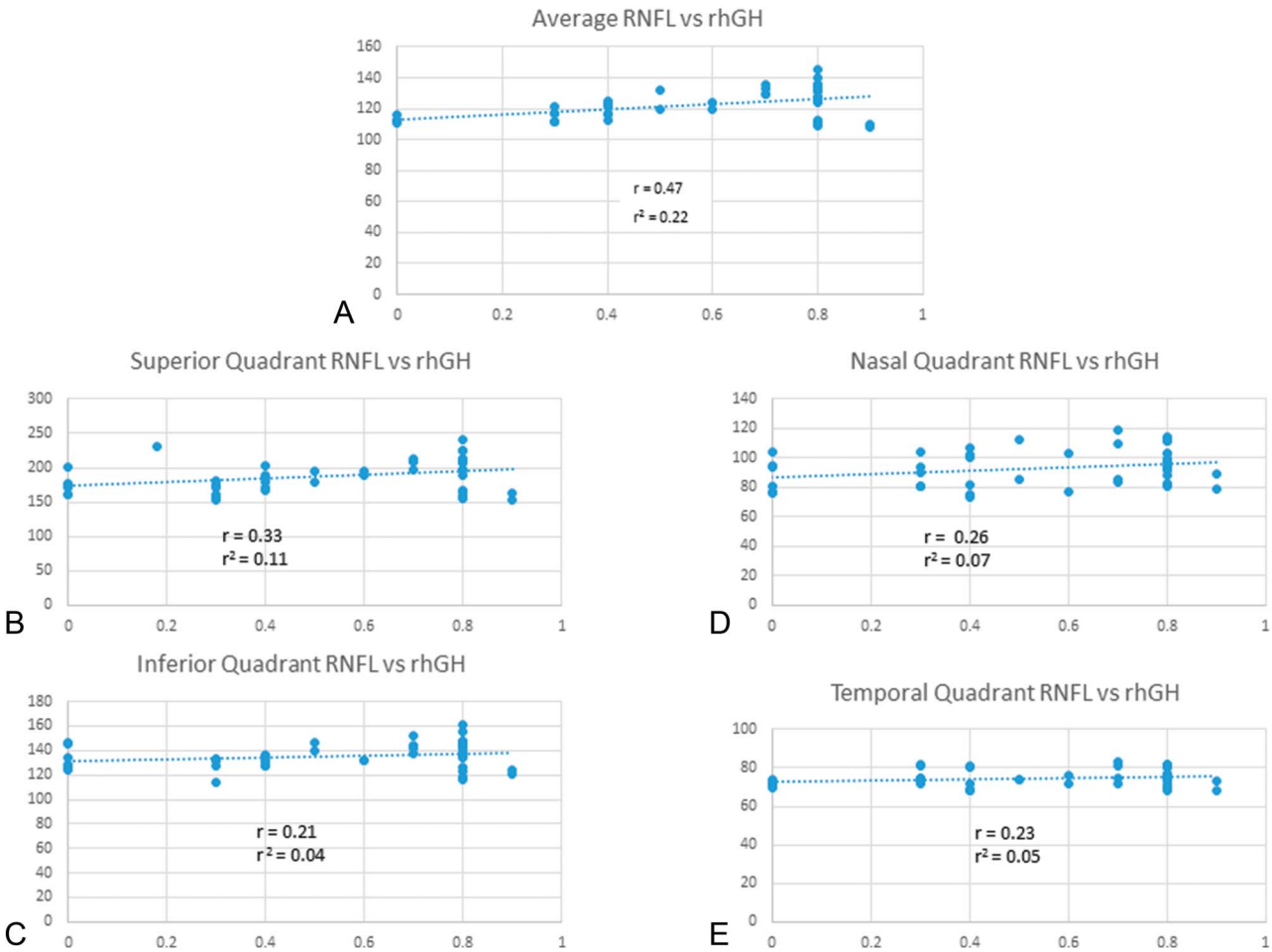

Fig. 6. A. Average RNFL values at different rhGH dosages, correlation graph with coefficient of correlation and determination values. Despite an overall positive correlation between rhGH dose and RNFL thickness was observed, it was not very strong ($r = 0.47$, $r^2 = 0.22$). **B–E.** Superior, inferior, nasal, and temporal quadrant average RNFL values at different rhGH dosages, correlation graph with coefficient of correlation and determination values. When the correlation was recalculated for each quadrant separately, the overall trend of positive but weak correlation between rhGH dose and RNFL thickness persisted.

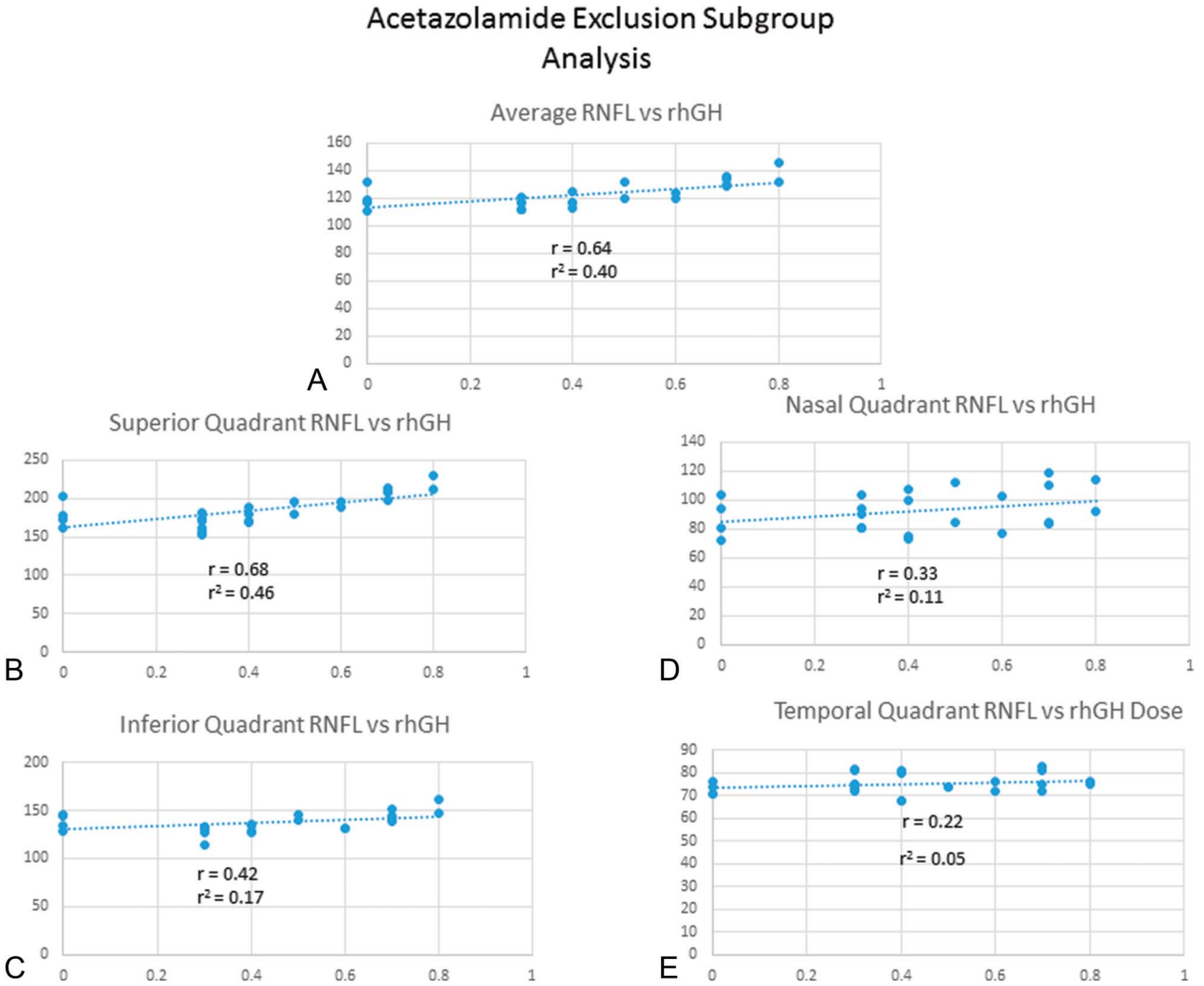

Fig. 7. Acetazolamide exclusion subgroup analysis. **A.** Average RNFL values at different rhGH dosages, correlation graph with coefficient of correlation and determination values after RNFL values under acetazolamide treatment were excluded. Removing RNFL values under acetazolamide treated further strengthened the positive correlation between rhGH dose and RNFL thickness ($r = 0.64$, $r^2 = 0.40$). **B–E.** Superior, inferior, nasal and temporal quadrant average RNFL values at different rhGH dosages, correlation graph with coefficient of correlation and determination values after RNFL values under acetazolamide treatment were excluded. When the correlation was recalculated for each quadrant separately, the strengthened positive trend persisted with exception of the temporal quadrant.

Although rhGH therapy is relatively safe and is associated with only few adverse effects,[5] it is essential to perform ophthalmic examination to detect PTCS and its detrimental effects on the eye.[5] In children, PTCS can be entirely asymptomatic and in early stages may present only with subtle papilledema.[6] When diagnosed at relatively later stages, studies have shown permanent loss of vision and visual field defects in up to 10% and 17% of children, respectively.[6] The pathogenesis of rhGH-induced PTCS remains relatively unknown. It is postulated to alter cerebrospinal fluid drainage across arachnoid villi.[6] It is also theorized that rhGH might be increasing cerebrospinal fluid production by the way of IGF-1 receptors.[7] Ophthalmoscopic examination of the fundus has been the gold standard for optic nerve evaluations.[3] However, this technique is limited because assessment is subjective and based on the training and experience of the physician, especially for subtle changes. A noninvasive adjunct evaluation tool, such as OCT, might therefore be valuable in the evaluation and follow-up of patients, especially children.

To the best of our knowledge, this is the first report in the literature that correlates OCT RNFL values with rhGH dose. As mentioned previously, there is a substantial amount of information in the literature showing the relationship between rhGH therapy and PTCS.[5,6] The literature also shows that OCT is reliable for the follow-up of PTCS and related papilledema.[2–4]

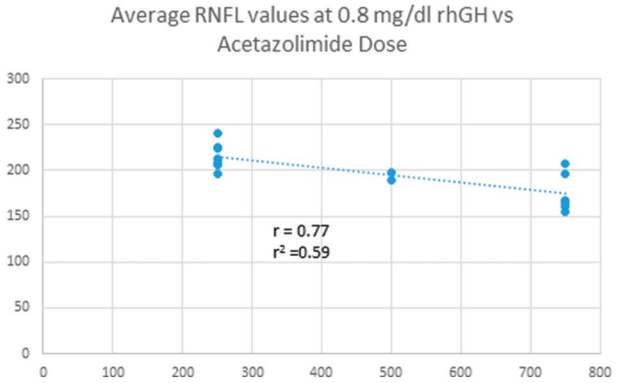

Fig. 8. Average RNFL values at 0.8 mg/dL with different acetazolamide doses, correlation graph with coefficient of correlation and determination values. Higher doses of acetazolamide resulted lower (i.e., thinner) RNFL values, indicating a very strong negative correlation ($r = 0.77$, $r^2 = 0.59$).

Our case report combines these two pieces of information from the literature.

We have found that the average RNFL values correlated well with rhGH, especially when acetazolamide's effect was not included in the calculations. When we studied each quadrant separately, all had a good correlation of RNFL values with rhGH dose. The correlation was higher in the superior and inferior quadrants compared with the nasal and temporal quadrants. This finding was consistent in both the general and acetazolamide exclusion groups. As reported in previous studies, we also found that higher doses of acetazolamide correlated with lower (thinner) RNFL values.[3]

Optical coherence tomography was used to measure RNFL thickness every 2 months or at each rhGH dose adjustment. In the case of PTCS after rhGH therapy, rhGH is usually stopped all together until resolution and restarted at a lower dose.[5] By contrast, we were able to titrate the dose precisely to prevent a flare-up of PTCS but without stopping it totally. The OCT was easy to use and accurately demonstrated even minor changes in the RNFL thickness.

In our case report, we observed a correlation between rhGH dose and RNFL thickness measured by OCT, especially when acetazolamide was excluded because of its confounding effect. If it can be verified in larger prospective and randomized trials, this finding could be an early sign of rhGH-induced PTCS. Early detection and careful management of patients who receive rhGH might be a preventative measure.

Key words: optical coherence tomography, recombinant growth hormone therapy, retinal nerve fiber layer.

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