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Nerve Growth Factor Eye Drops for Optic Pathway Gliomas: Four-Year Follow-Up Findings in Children After a Single Treatment Course

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Research Article

Keywords: nerve growth factor, optic pathway glioma, neurofibromatosis type 1, visual function, neuroprotection

Posted Date: July 29th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10466798/v1

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Journal of Neuro-Oncology on September 1st, 2026. See the published version at https://doi.org/10.1007/s11060-026-05777-z.

Abstract

Purpose.

A previous double-blind, randomized, placebo-controlled, phase II clinical trial reported beneficial effects of a short-term treatment (10 days) with murine nerve growth factor (mNGF) eye drops on visual function in children with optic pathway gliomas (OPG). The present study aimed to evaluate long-term changes in clinical and neuroradiological parameters in the cohort of OPG patients who had previously participated in the phase II mNGF trial.

Methods.

Fifteen of the 18 patients originally enrolled in the phase II mNGF trial agreed to undergo clinical and neuroradiological monitoring over a 48-month follow-up period. Every 6 months, patients underwent general clinical and neuro-ophthalmological examination, visual evoked potentials (VEP), and photopic negative response of the electroretinogram (PhNR). Brain MRI was performed every 12 months.

Results.

Comparison of initial and final follow-up median values revealed no statistically significant changes in visual acuity, VEP amplitude, PhNR amplitude, or visual field radius. No significant differences were observed in any parameter relative to baseline values of the mNGF trial. Furthermore, no significant between-group differences were detected during follow-up when comparing patients initially assigned to mNGF versus placebo. Brain MRI demonstrated stable disease in all patients throughout the observation period.

Conclusion.

These findings indicate favorable long-term safety and tolerability of a short-term course of topical mNGF in children with OPG, with sustained visual and neuroradiological stability over four years. Further prospective clinical studies are needed to confirm both the short- and long-term clinical efficacy of NGF treatment in preventing OPG-induced visual loss.

Introduction

Optic pathway gliomas (OPGs) of childhood are low-grade gliomas (LGG) arising anywhere along the optic pathway and account for 3–5% of all pediatric brain tumors. In the pediatric population, OPGs are typically pilocytic astrocytomas (WHO Grade I) characterized by slow progression over many years and an excellent overall survival [1]. Most affected patients are affected by Neurofibromatosis type 1 (NF1), and approximately 15–20% of children with NF1 will develop these tumors during their lifetime [2].

Despite high survival rates, OPGs are associated with significant morbidity. Clinical manifestations depend on tumor location; progressive visual loss is generally regarded as the most common and debilitating consequence in both sporadic and NF1-associated OPGs [3]. Visual impairment can profoundly affect children's quality of life and neurodevelopment, making preservation of visual function a central goal of therapeutic management [4]. Current treatment modalities — radiotherapy (for children older than 8 years) or chemotherapy regimens (for younger children), as per the SIOP LGG 2004 protocol — are primarily aimed at controlling tumor growth. Notably, no disease-specific treatment is currently available to address OPG-induced visual dysfunction.

Children with OPG often exhibit thinning of the retinal nerve fiber layer (RNFL) due to retinal ganglion cell (RGC) apoptosis, a process closely associated with progressive visual impairment [5]. In NF1-associated OPG, RGC apoptosis may result not only from direct mechanical compression of the optic pathway by the tumor mass but also from a functional deficit caused by the loss of neurofibromin. This loss-of-function leads to hyperactivation of the Ras pathway, phosphorylation of atypical protein kinase C (PKC), and reduction in intracellular cyclic adenosine monophosphate (cAMP) levels [6, 7]. Importantly, preclinical studies have shown that in rodent models RGC apoptosis is preceded by a phase of axonal damage, defining a potential therapeutic window during which intervention could attenuate irreversible cell loss [8, 9]. The work of Toonen et al. identified a clinically relevant time window for future therapeutic strategies aimed at preserving RGC function in NF1-associated OPG [8].

Several preclinical investigations [10–12] and clinical trials in OPG patients [13, 14] have demonstrated the potential of nerve growth factor (NGF), a prototypical neurotrophin, to preserve and protect visual function. NGF mediates its biological effects through two classes of cell-surface receptors: the high-affinity tyrosine kinase receptor TrkA and the low-affinity p75 neurotrophin receptor (p75NTR) [15]. Both receptors are expressed throughout the visual system, from the retina to the visual cortex. In the retina, TrkA and p75NTR are present on RGCs, where endogenous NGF is physiologically produced and serves as a survival factor for these neurons [11].

The potential therapeutic benefit of murine NGF (mNGF) on visual function in OPG was previously assessed in a randomized, double-blind, placebo-controlled phase II clinical trial [14]. Eighteen OPG patients (age range 2–23 years, with and without NF1), presenting with stable disease and severe visual impairment, were randomly assigned to receive either topical mNGF (0.5 mg eye drops administered three times daily for 10 consecutive days; n = 10) or a matched placebo formulation (n = 8). Outcome measures at baseline and at days 15, 30, 90, and 180 included visual acuity, visual field, VEP, optical coherence tomography (OCT), and the photopic negative response of the electroretinogram (PhNR); MRI was performed at baseline and day 180. Treatment with mNGF led to statistically significant improvements in electrophysiological parameters (PhNR amplitude and VEP) compared with placebo. Additionally, a notable enlargement of the visual field was observed in treated patients in whom reliable measurement was feasible. No severe ocular or systemic adverse events were recorded; mNGF treatment was considered safe and well tolerated. MRI demonstrated no tumor progression in either group [14].

Following completion of the phase II trial, 15 of the 18 patients agreed to undergo an extended off-treatment clinical, functional, and neuroradiological follow-up lasting to 48 months. The primary objective of this extended observation was to evaluate the long-term changes in clinical and neuroradiological parameters in this unique cohort of OPG patients previously exposed to experimental NGF treatment. Here we report the clinical outcomes obtained during the extended follow-up, encompassing visual function results and neuroradiological assessments.

Methods

Study Population

Fifteen of the 18 patients (or their legal guardians) who had participated in the original mNGF phase II clinical trial provided consent to undergo extended clinical and neuroradiological monitoring for up to 48 months [14]. Written informed consent was obtained from the participating patients, caregivers, or legal guardians. The study protocol was approved by the Ethics Committee of the Sacred Heart Catholic University in Rome (03/07/2012 – N. P/659/CE/2012). Clinical and demographic characteristics of these patients at the time of study entry into the extended follow-up are reported in Table 1. Ten of the 15 patients had severe visual impairment at baseline. The extended follow-up commenced within 6 months after the conclusion of the original mNGF trial.

Table 1
Demographic and clinical characteristics of enrolled patients (N = 15).

Characteristic	Value
Sex: Male, n (%)	6 (40.0%)
Sex: Female, n (%)	9 (60.0%)
NF1, n (%)	11 (73.3%)
Age at enrolment, median (range), years	12.6 (2.6–24)
Time from diagnosis to study entry, median (range), years	7.1 (1.8–19.6)
Prior biopsy/surgery, n (%)	6 (40.0%)
Prior chemotherapy, n (%)	13 (86.7%)
Assigned to mNGF in phase II trial, n (%)	9 (60%)
Assigned to placebo in phase II trial, n (%)	6 (40%)

NF1, Neurofibromatosis type 1; mNGF, murine nerve growth factor; n, number of patients.

Clinical Assessments

Every 6 months, patients underwent a comprehensive general clinical and neuro-ophthalmological examination, including measurement of visual acuity (Snellen chart), Goldmann perimetry for visual field assessment, flash visual evoked potentials (VEP), and photopic negative response of the electroretinogram (PhNR). Brain MRI was performed every 12 months.

Neuroradiological Assessment

Neuroradiological evaluations were performed by board-certified pediatric neuroradiologists according to the Response Assessment in Neuro-Oncology (RANO) criteria for low-grade glioma [16]. Progressive disease (PD) was defined by any of the following: (1) development of new lesions or detection of abnormal contrast enhancement on follow-up MRI, suggestive of malignant transformation; (2) an increase of ≥ 25% in tumor volume on T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences; or (3) progressive clinical or visual deterioration not attributable to treatment-related adverse effects. Patients exhibiting tumor volume changes of less than 25% without clinical deterioration were classified as stable disease (SD).

Statistical Analysis

Data are expressed as median values with ranges unless otherwise stated. Statistical comparisons of longitudinal data were performed using the Wilcoxon signed-rank test for non-parametric paired data. Between-group comparisons (mNGF versus placebo) were performed using the Mann–Whitney U test. A p-value < 0.05 was considered statistically significant for all analyses.

Results

Patient Characteristics

Demographic and clinical characteristics of the 15 enrolled patients are summarized in Table 1. Eleven of the 15 patients (73.3%) carried an NF1 diagnosis. The median age at study enrolment was 12.6 years (range: 2.6–24 years). The median time from initial OPG diagnosis to study entry was 7.1 years (range: 1.8–19.6 years). Thirteen patients (86.7%) had previously received chemotherapy; six patients (40%) had undergone prior surgical resection.

Visual Acuity

Visual acuity results for each patient are reported in Table 2. For patients in whom reliable assessment was feasible, initial (baseline) and final follow-up Snellen decimal values are presented for both eyes. Wilcoxon signed-rank analysis revealed no statistically significant change in median visual acuity when comparing baseline and end-of-follow-up values (p = ns). At the individual level, a clinically meaningful

decline (> 3 lines) was observed in the left eye of patient #5, whereas a clinically meaningful improvement (> 3 lines) was noted in the left eye of patient #14.

Table 2
Visual acuities (Snellen decimal) recorded at baseline and at the end of follow-up.

Patient	Group	Visual Acuity RE (Baseline / End)	Visual Acuity LE (Baseline / End)
1	P	1.0 / 0.7	0.001 / 0.001
2	P	0.04 / 0.04	0.001 / HM
3	P	LP / LP	LP / LP
4	P	0.005 / 0.005	1.0 / 1.0
5	P	HM / HM	0.8 / 0.1 ↓
6	P	0.02 / 0.02	0.05 / 0.05
7	mNGF	HM / HM	0.8 / 0.6
8	mNGF	1.0 / 1.0	1.0 / 1.0
9	mNGF	0.01 / 0.01	0.01 / 0.01
10	mNGF	0.01 / 0.01	0.01 / 0.01
11	mNGF	1.0 / 1.0	1.0 / 1.0
12	mNGF	LP / LP	LP / LP
13	mNGF	LP / LP	LP / LP
14	mNGF	1.0 / 1.0	0.02 / 0.2 ↑
15	mNGF	0.05 / 0.05	0.1 / 0.1

RE, right eye; LE, left eye; P, placebo group; mNGF, treated group; LP, light perception; HM, hand motion; ↑ improvement > 3 Snellen lines; ↓ decline > 3 Snellen lines. Ages are reported at first and last visit.

Visual Evoked Potentials

Flicker VEP amplitude results are illustrated in Fig. 1, presented as box plots of amplitude distribution for the right and left eye at baseline and at the end of follow-up. No statistically significant change in median VEP amplitude was detected (p = ns). VEP phase remained stable throughout the observation period (baseline median: 103°; end-of-follow-up median: 108°; p = ns).

Photopic Negative Response

PhNR amplitude data are presented in Fig. 2 as box plots of amplitude distribution for the right and left eye, recorded at baseline and at the end of follow-up. No statistically significant change in median PhNR amplitude was detected across the follow-up period (p = ns). PhNR implicit time likewise showed no significant variation.

Visual Field

Goldmann visual field results, expressed as the major radius in degrees, are reported in Table 3 for patients in whom reliable perimetric testing was achievable. Values at baseline, at 3 months post-treatment (as previously reported in the phase II trial [14]), and at the end of the extended 48-month follow-up are presented. Wilcoxon signed-rank analysis showed no statistically significant change in median visual field radius when comparing baseline and 48-month values (p = ns).

Table 3
Goldmann visual field results expressed as major radius (degrees) recorded at baseline, 3 months post-treatment, and 48 months post-treatment.

Patient	Group	Baseline (deg)	Post-treatment 3 months (deg)	Post-treatment 48 months (deg)
1	P	24.9	18.9	19
2	P	26.5	17.4	17
3	P	15	12	9
4	P	13	12	12
5	P	20	18	11
6	P	11	10	10
7	mNGF	17.3	21.9	18
8	mNGF	12.4	20.6	15
9	mNGF	3.6	20.8	10
10	mNGF	2.8	5.2	6
11	mNGF	10.6	24.4	12
12	mNGF	8.5	20.2	20
13	mNGF	11	16	12
14	mNGF	9.8	11.2	10
15	mNGF	9	13	9

P, placebo group; mNGF, treated group..

Neuroradiological Outcomes

Brain MRI showed no significant change in tumor volume throughout the extended follow-up in any of the enrolled patients. Two patients (patients #5 and #8) exhibited a minor volumetric increase of approximately 10% on follow-up imaging; however, these changes did not meet the RANO criteria for progressive disease and were classified as stable disease. Figure 3 displays representative MRI scans acquired at baseline (upper row), shortly after mNGF administration (middle row), and after four years of follow-up (lower row), illustrating different sites of optic pathway involvement: optic nerve (left column), optic chiasm (middle column), and retrochiasmatic region (right column). For each case, both enhancing and non-enhancing tumor components were evaluated. Stable disease was confirmed in all cases at the four-year follow-up.

Discussion

The present study reports the four-year clinical and neuroradiological outcomes of children with OPG who had previously received a short-term course of topical mNGF in a randomized phase II trial. The principal findings indicate sustained stability of all assessed visual function parameters — including visual acuity, VEP amplitude, PhNR amplitude, and visual field, as well as stable neuroradiological status, over an extended observation period. These results collectively support the favorable long-term safety profile of topical NGF in pediatric OPG.

The neuroprotective properties of exogenous NGF on RGC viability have been well established in preclinical models. Administration of mNGF has been shown to attenuate RGC apoptosis following optic nerve transection and ocular ischemia [10, 17, 18]. The molecular basis of this neuroprotective effect likely involves NGF–TrkA signaling, which upregulates the anti-apoptotic mediator BCL-2 and suppresses caspase activation [19]. In support of this mechanism, Sivilia et al. demonstrated that a single intravitreal NGF injection in a rat model of permanent carotid artery occlusion prevented RGC degeneration by modulating the Bax/BCL-2 ratio and c-Jun expression [18].

More recent preclinical studies using optic nerve crush (ONC) rat models have extended these findings, demonstrating that both intravitreal recombinant human NGF (rhNGF) and rhNGF eye drop formulations can promote axonal regrowth and reduce RGC loss. The proposed mechanism involves interference with apoptotic pathways, including inhibition of the NogoA/p75NTR complex, suppression of Rho/ROCK2 signaling, and modulation of axonal growth-inhibitory pathways [12].

A potential concern regarding the therapeutic use of NGF in OPG relates to the theoretical risk of pro-proliferative effects on neoplastic glial tissue. However, converging in vitro and in vivo evidence suggests that this risk is low in the context of pediatric pilocytic astrocytomas. These tumors are characterized by downregulation of TrkA — the receptor whose activation is associated with neoplastic cell proliferation and survival — and by upregulation of the pro-apoptotic p75NTR receptor [20]. This receptor profile may partly explain the characteristically indolent behavior of LGGs and may even support a differentiating role of NGF on LGG cells. Indeed, in vitro studies have demonstrated that NGF inhibits rat C6 glioma cell proliferation and promotes cellular differentiation, evidenced by morphological changes, cellular

hypertrophy, and growth cone formation [21], findings subsequently confirmed in vivo [22]. More recently, Meco et al. showed that NGF treatment prevents proliferation of pediatric LGG cell lines through induction of cellular senescence [23].

The stable MRI findings observed across the four-year follow-up are consistent with the established natural history of pediatric pilocytic astrocytomas, which typically exhibit prolonged periods of neuroradiological quiescence [1]. Importantly, the two patients who displayed minor volumetric increases (approximately 10%) did not meet RANO criteria for progressive disease, and neither experienced significant clinical deterioration, reinforcing the classification of stable disease for all cases.

Several limitations of this study warrant acknowledgment. The cohort size was small (n = 15), reflecting the rarity of the condition and the pragmatic constraints of recruiting from a completed phase II trial. No new control group was established for this extended follow-up, and the absence of randomization in the observational phase precludes definitive inferences regarding treatment-specific long-term effects. Additionally, optical coherence tomography, a sensitive marker of RNFL thickness and RGC integrity, was not systematically included in the extended follow-up protocol, representing a missed opportunity for structural-functional correlation.

In conclusion, this extended four-year follow-up of children with OPG demonstrates the sustained safety and favorable tolerability of topical mNGF administered as a single short-term treatment course. The observed neuroradiological and functional stability over time provides reassurance regarding the absence of long-term adverse effects, including tumor stimulation, associated with this treatment. Future prospective, adequately powered clinical studies with standardized outcome measures will be necessary to conclusively establish the short- and long-term clinical efficacy of NGF therapy in preventing OPG-induced visual loss.

Declarations

Author Contributions

B.F. and A.R.: Study conception and design, and critically revised the manuscript. B.F., G.A. G.P. E.D'A., S. M., T.V., A.A., and A.R..: Manuscript writing, data analysis, literature review, data collection, radiological review, and follow-up of the patients. G.A., S.M., T.V., G.P., E D'A., A.A., B.F., and A.R. Data collection and follow-up of the patients. All authors read and approved the final manuscript.

Funding

No funding was received for this study.

Competing interests

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Sacred Heart Catholic University in Rome (03/07/2012 – N. P/659/CE/2012).

Consent for publication

The authors affirm that the brain scan images presented in Fig. 3 have been entirely de-identified. As no potentially identifying information is present, specific informed consent for publication was not required.

Data Availability

The data that support the findings of this study will be made available upon reasonable request.

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Figures

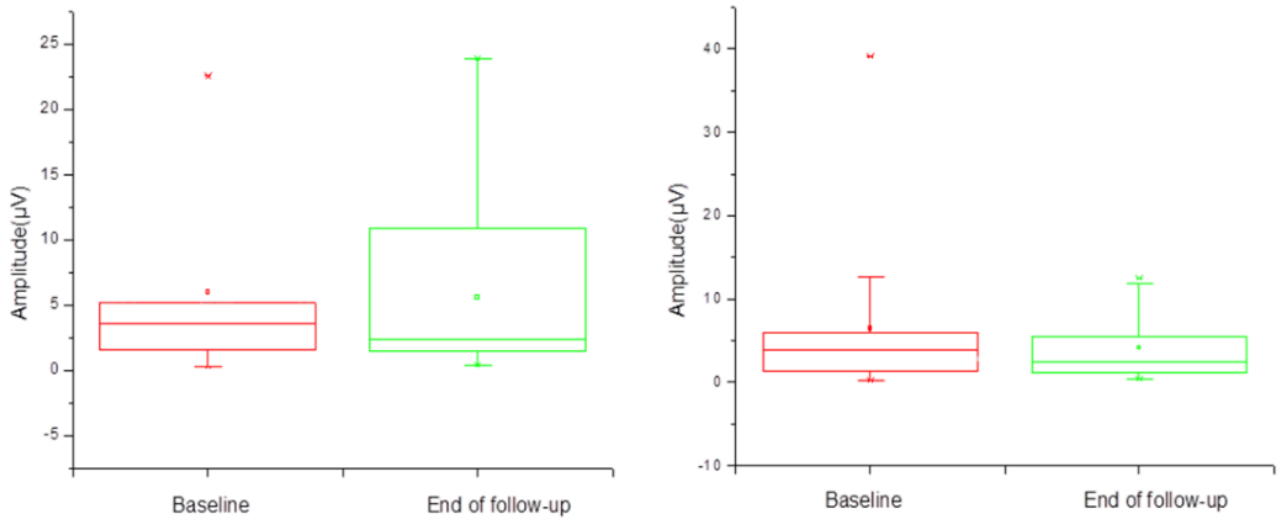


Figure 1

VEP amplitude results, expressed as box plots, recorded at baseline and at the end of follow-up

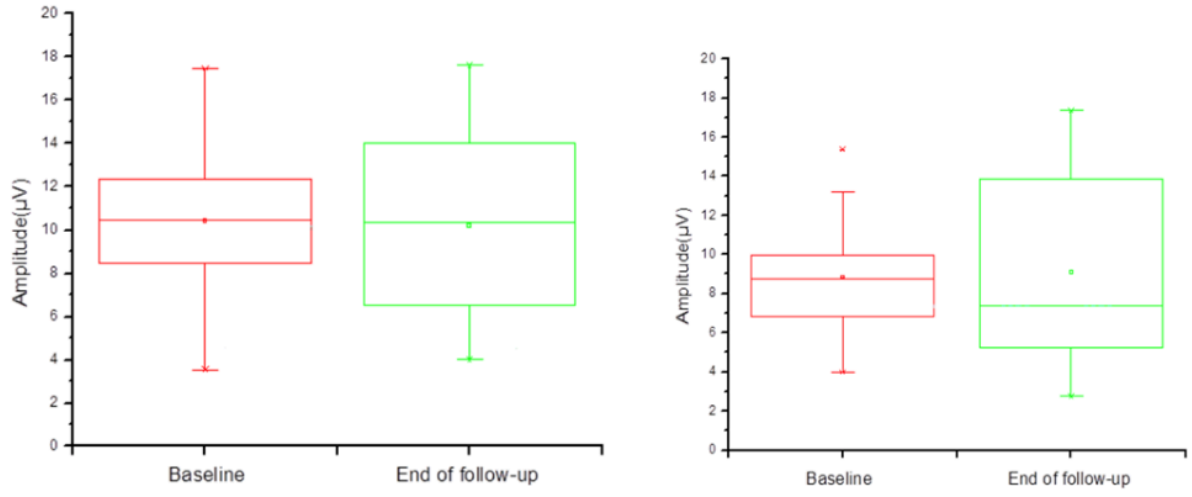


Figure 2

PhNR amplitude recorded at baseline and at the end of follow-up]

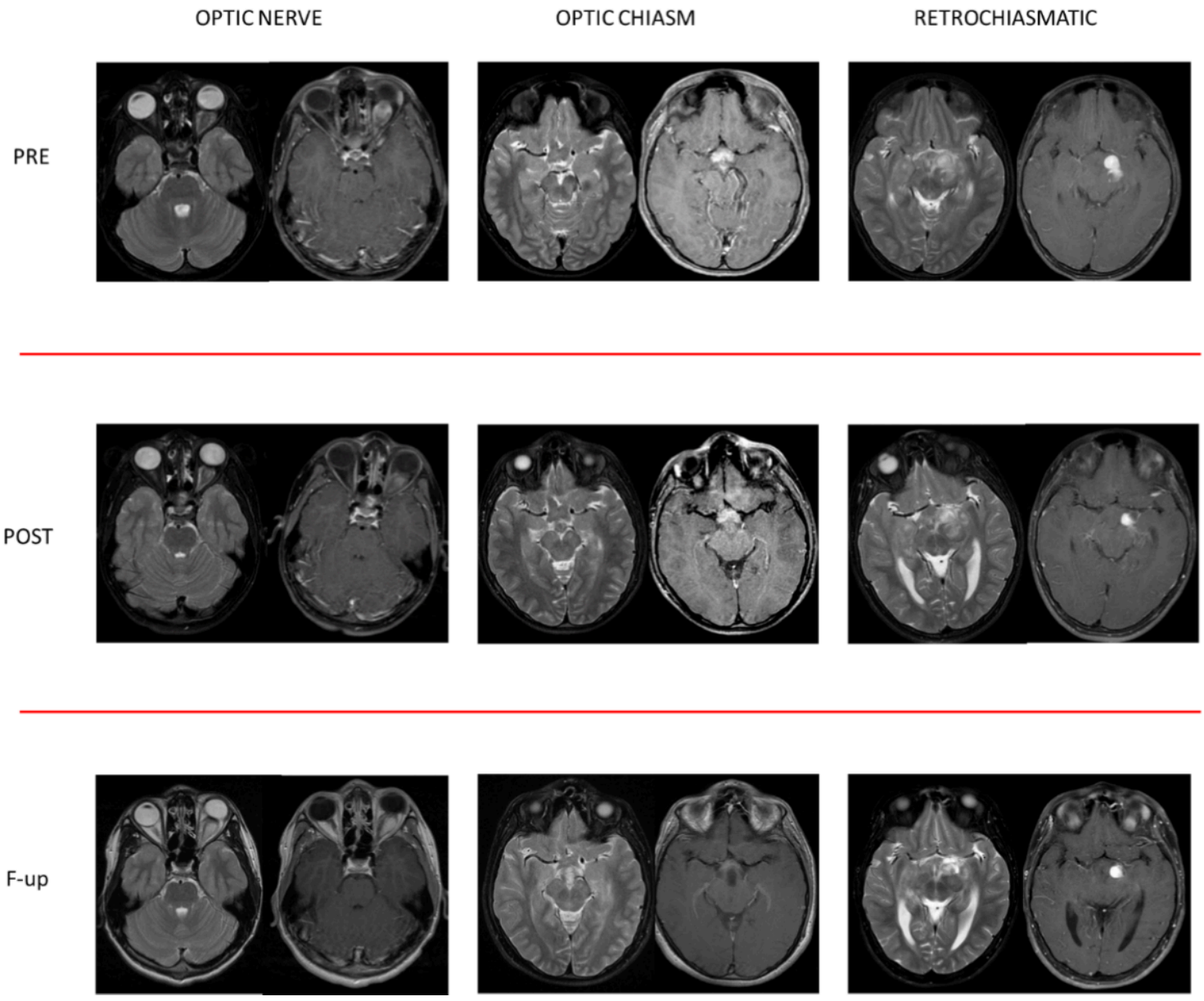


Figure 3

Brain MRI of OPG patients acquired at baseline (upper row), shortly after mNGF administration (middle row), and after four years of follow-up (lower row), illustrating optic nerve (left), chiasmatic (middle), and retrochiasmatic (right) involvement