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# Pretreatment Endocrine Disorders Due to Optic Pathway Gliomas in Pediatric Neurofibromatosis Type 1: Multicenter Study

| This is a pre print version of the following article:   |
|---|
| Original Citation:  |
|   |
|   |
|   |
| Availability:   |
| This version is available http://hdl.handle.net/2318/1767404 since 2021-01-19T10:24:50Z   |
|   |
|   |
| Published version:  |
| DOI:10.1210/clinem/dgaa138  |
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# Pre-treatment endocrine disorders due to the optic pathway gliomas in children with neurofibromatosis type 1: multicenter study on prevalence and predictive factors

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## Short title: endocrine disorders in children with NF1 related OPG

### Key words: Optic pathway glioma, NF1, endocrine disorders, hypothalamus

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Financial support: nothing to declare.

Disclosure summary: nothing to declare.

#### ABSTRACT

**Context:** Up to 20% of children with Neurofibromatosis type 1 (NF1) develops low-grade gliomas affecting of the optic pathway (OPG) that can result in neuroendocrinopathy. Literature on prevalence and type of endocrine disorders in NF1 related OPGs is scarce.

**Objectives:** The aim of the study was to determine prevalence of endocrinopathies and to investigate predicting factors in patients with NF1 related OPGs before any treatment. We particularly hypothesized that endocrinopathies were strictly associated with the tumors localization.

**Design:** multicenter retrospective study

**Settings and patients**: Records were reviewed for 116 children with NF1 and OPG followed at 4 Italian centers.

**Main outcome measures:** We studied those endocrinopathies occurring before radio- and chemotherapy and/or surgery. OPGs were classified according to the modified Dodge classification (MDC).

**Results:** Thirty two children (27.6%) had neuroendocrinopaties. Central precocious puberty (CPP) was diagnosed in 23 children (71.9%), GH deficiency (GHD) in 3 children (9.4%), diencephalic syndrome (DS) in 4 (12.5%), hyper-secretion of GH (GHH) in 2 (6.2%). In a multivariate cox regression analysis, hypothalamic involvement was the only independent predictor of endocrine disorders (HR: 5.02 (1.802-13.983); p 0.002).

**Conclusions:** Endocrine disorders were common in patients with NF1 and OPGs independently from any treatment.

In our experience CPP was the most prevalent endocrine disorder while GHD was not common as previously described. DS and GHH, although rare, can occur in patients with NF1 and OPGs. Tumour location was the most important predictor of endocrine disorders, particularly hypothalamic involvement. Hence, physicians should bear in mind that patients with OPGs involving the hypothalamic region should be subjected to careful auxological evaluation.

#### Introduction

Neurofibromatosis type 1 (NF1) is a multisystemic, autosomal dominant condition, associated to neuro-oncological risk. It is due to heterozygous mutations of the NF1 oncosuppressor gene located on chromosome 17q11.2 which leads to secondary increased mTOR activation (1). Its product, neurofibromin, is highly expressed in Schwann and glial cells.

This explains why up to 15% of NF1 patients develops a brain tumor (2), with optic pathway glioma (OPG) representing the commonest one occurring in about 20% of patients within the first decade of life (3). OPG is considered a hallmark of NF1, so much that it represents one of the diagnostic criteria together with cafè-au-lait macules (CALMs), freckling, neurofibromas, Lisch nodules, bone dysplasia and a first-degree relative affected.

OPGs can have different histology (i.e. LGSI, DA, pilomyxoid astrocytoma and ganglioglioma), however, in almost all NF1 cases, they present as a pilocytic grade 1 astrocytoma and usually tend to be more indolent than in sporadic forms, and to involve more frequently the anterior part of the optic pathway, bilaterally, with chances of spontaneous regression (4–12).On the other hand, about half of patients becomes symptomatic and needs to be treated (surgically and/or with chemotherapy). In fact, OPG (13) may cause visual loss, endocrine disorders and can exceptionally lead to death (14).

Even if endocrine disorders have been reported in 1% to 3% of all NF1 patients (15–17), literature about prevalence, types and outcomes of OPG related endocrinopathies is extremely scarce with just two paper published on this topic at the best of our knowledge (15, 17).

#### **Objectives**

The aim of our study was to determine prevalence of endocrinopathies in patients with NF1 related OPGs before any treatment and to investigate their predictors, especially in relation to tumour location and hypothalamic involvement.

#### Methods

#### Study cohort

This retrospective, multicenter study included patients followed at 4 Italian tertiary pediatric referral centres for NF1: Pediatric Referral Centre of Neurofibromatosis of Università degli Studi della Campania, Istituto G. Gaslini of Genoa, Meyer' Children Hospital of Florence, Pediatric Endocrinology, Regina Margherita Children Hospital, University of Turin (52 cases from Naples, 25 from Turin, 20 from Florence, and 19 from Genoa).

Patients with a clinically confirmed diagnosis of NF1 (18), and radiological diagnosis of OPG performed before the age of 16, were included.

Gender, NF1 inheritance, age at diagnosis of NF1 and of OPG, indications for diagnostic MRI scan, duration of follow up were recorded.

OPGs were classified according to the modified Dodge classification (MDC), also known as PLAN classification (10) (Table 1). Particularly, a neuro-radiologist (MC) with expertise in this field, reviewed magnetic resonance imaging (MRI) scans performed at diagnosis.

OPGs involving the optic nerves were recorded as MDC1, MDC 2 was assigned to chiasmatic OPGs, whereas tumours involving tracts and radiations were staged as MDC 3. The highest (most posterior) MDC stage was assigned in cases of tumours involving multiple regions, as in previous studies (19).

Primary treatment approaches were recorded as surgical resections (any tumor debulking, decompression procedures (aimed at relieving raised intracranial pressure), radiotherapy, chemotherapy and wait and see strategy. Chemotherapy was administered according to SIOP trial protocols.

Definitions of endocrine diseases

We included in the analysis endocrinological disorders that only occurred prior to any therapy (either surgery or chemotherapy).

Central precocious puberty (CPP) was defined as breast budding before the age of 8 years in girls and testicular volume >4 ml before the age of 9 years in boys, together with pubertal basal LH levels and/or GnRH-stimulated (0.1 mg Relefact LHRH, Sanofi-Aventis, Frankfurtam Main, Germany) LH levels >5 IU/l.

GH hyper secretion (GHH) was diagnosed in presence of linear growth acceleration, elevated IGF-1 levels for age (adjusted for sex and pubertal stage), and lack of GH suppressability to <1.0 ng/ml during oral 1,75 g/kg glucose tolerance test.

GH deficiency (GHD) was defined as decreased height velocity over a period of at least 6 months in the absence of other causes, with a GH peak <10 ng/ml until December 2014 and <8 ng/ml on two different provocative test (arginine, clonidine, ITT and glucagon test were used).

Diencephalic syndrome was defined as failure to thrive , not explained by vomiting, diarrhea, decreased caloric intake or other causes, and /or Hypothalamic involvement confirmed at the time of diagnosis, and/or crossing down of 2 percentiles for weight with a normal growth rate, and/or BMI <-2 SD and/or emaciation, euphory, overactivity. (20–22).

For all children with endocrine disorders we recorded age at onset and type of the endocrine disorder, auxological data, hormonal testing results, and specific treatment needed.

The local ethical committees approved the study. Informed consent was obtained by patients, or by their parents/tutors.

#### **Statistics**

Differences between groups were analyzed with Mann-Whitney U-test for continuous non parametric variables. Numbers and proportions were compared using chi-squared test. Kaplan- Meier analysis was run in order to determine endocrine event free survival from diagnosis and log-rank test was used to compare curves of patients with and without hypothalamic involvement . Only the first endocrine disorder occurred before any treatment was included in the analysis. Patients who did not develop any endocrine disorders were censored at treatment start time and at last follow up for the ones who did not receive any treatment at all. Univariate and multivariate Cox regression models were used to explore predictors of endocrine disorders before any treatment. Variables statistically significant in the univariate analysis were included in the multivariate one: MDC stage, hypothalamic involvement and age at diagnosis of OPGs. P values <0.05 were considered statistically significant.

SPSS 23 software for Windows for Windows was used for all statistical analysis.

#### Results

#### **Study population**

We enrolled a total number of 116 children (52 M) with NF1 (age at diagnosis 1.75 years (range 0-12.25 years) and OPG (age at diagnosis 4.17 years (range 0.42-13.75). Median NF1 follow-up was 9 years (range: 0.2-35).

Table 1 summaries patients' demographic data, NF1 and OPGs features, details about diagnosis, treatment and follow-up. The above-mentioned data are also separately reported for patients with and without endocrine diseases.

Endocrine disorders were identified in 31 (26.7%) children.

OPGs were diagnosed earlier in patients with endocrine disorders respect of compared to those without (median age at diagnosis of 3.3 years (range 1.33-11.92) vs 4.71 years (range 0.42-13.75), p 0.03). The median duration of OPGs follow-up was 7.9 years (0.5-24.5 range).

Almost half of patients (49, 42.7%) underwent brain MRI for screening. Other indications to MRI scan were: visual symptoms (34.5%), headaches (2.5%), neurological signs (1.8%), plexiform neurofibromas (0.8%). Eight children (6.8%) underwent brain MRI because of clinical suspect of endocrinopathies, and four of them (3.4%) were subsequently confirmed to suffer from endocrine disorders (2 CPP, 1 DS, 1 GHH) (Table 1).

Regarding tumor location, 33.6 % of patients (39) were staged as MDC1, 19.8% as MDC 2 (23), 46.6% (54) as MDC3/4. In particular, anterior part of the pathway was almost always involved

(93.1%), followed by the chiasm (62.3%) and the posterior tracts (45.2%). No cases of leptomeningeal metastasis were observed. Tumors involving hypothalamus represented 33.6% of all OPGs: 39 cases, 6 of which classified as MDC2, 33 as MDC3. Worthy of remark, none of the patients with nerve involvement only (MDC1) presented endocrine disorders. Besides, we observed a statistically significant difference in percentage of hypothalamic involvement between patients with and without endocrinopathies: 78.1% vs 16.7% (p=0.000) (Table 1).

Among patients with endocrine disorders, the proportion of patients who later underwent treatment for OPGs (both chemotherapy and/or surgery) was higher than in those without endocrine disorders (75.6%vs34.2%; p=0.0001).

#### **Endocrine disorders**

We identified 31 patients with endocrine disorders before any treatment. CPP was diagnosed in 23 children (72 %; 12 males, median age at diagnosis 8.2 years); GHD in 3 (9%; 3 males, median age at diagnosis 9.45 years); DS in 4 (12%; all females, median age at diagnosis 4.7 years) and GHH in 2 patients (6%; 2 females, median age at diagnosis 4 years). The median time of follow-up diagnosis of endocrine disorders from OPG onset was 4.58 years (range 0.08-8.17). Age at diagnosis of endocrine disorders was different according to type of disease, being lower in patients with DS and GHH (Table 2).

All patients with CPP were treated with GnRH analogs; all three patients with GHD were treated with growth hormone, two of them for a relatively short period of time (7 months, and 42 months) while one patient is still on therapy. One of the two patients with GHH was treated with octreotide acetate for 1 year, the other one did not received any treatment, since GHH was a transient phenomenon.

Children with endocrine disorders collectively received 9 surgeries (7 debulkings and 2 surgeries of hydrocephalus).

Considering the entire population, the cumulative proportion of patients free from endocrine disease –before any kind of treatment- at 10 years of follow-up was 65.9%. Endocrine event free survival declined up to 8 years post OPGs diagnosis (Figure 1S). Patients with hypothalamic involvement had a significant lower endocrine event free survival (p:<0.0001; Figure 1)

#### **Predicting factors**

Hypothalamic involvement, MDC stage and age at OPG diagnosis less than 5 years were independent predictors of endocrine disorders (table 3), whereas hypothalamic involvement was the only statistically significant predictor of endocrine disorder before any treatment in the multivariate analysis, HR 5.02 (1.802-13.983) p 0.002 (Table 3).

#### Discussion

Our study is the largest reported to date, focused on endocrinopathies occurring in children with NF1 related OPGs before treatment. We reported a considerable prevalence of endocrinological complications in OPGs (26.7%) before any treatment.

Some authors had published on endocrine disorders and NF1 children with or without OPGs (15,23).

Cnossen et al. reported a prevalence of endocrinologic disorders of 5% (6 / 122 children ) (15); 3/122 (2.5%) CPP (1/3 with chiasma glioma), 3/122 (2.5%) GHD (1/3 with chiasma glioma ). Overall 2/15 (13%) patients with chiasma glioma developed CPP or GHD. The author did not specify whether hypothalamus was involved (15).

Habiby et al. reported prevalence of precocious puberty and its relationship to OPGs in a cohort of 219 children with NF1(23). CPP was diagnosed in seven patients (3%), intriguingly all of them had OPGs involving the optic chiasm and 7/18 patients (39%) with chiasm involvement had CPP. Authors did not further discuss eventual hypothalamic involvement neither the occurrence of other endocrine disorders.

Studies investigating prevalence of endocrine disorders among patients with optic gliomas instead tended to include both patients with and without NF1 (19,24,25), making difficult to extrapolate data on prevalence. Moreover, they focused mostly on treatment related endocrine sequeale. At the best of our knowledge, only Sani and Albanese investigated prevalence of endocrine disorders in children with NF1 and OPGs before any treatment (17). They retrospectively reviewed a small cohort of 36 patients, founding endocrinopathies in 20 patients (55.6%). This prevalence was very high, even compared to studies on optic gliomas in mixed population (19).

Our data showed that the most prevalent endocrine disorder in NF1 patients with OPGs before any treatment was CPP. This data is in accordance with other studies on brain tumors involving hypo-thalamic region (20). Moreover, males are more affected than in idiopathic CPP (12:11), confirming previous studies (14).

GHD in our population was instead quite rare (3.4%), differently from the manuscript by Sani et Albanesi (17). In fact GHD was the more prevalent disorder in their population. Of note, all their cases of GHD were diagnosed with a single stimulation test and were not confirmed at retesting after adult height achievement. In other studies including patients with optic gliomas, GHD was mostly diagnosed after treatment and in particularly related to radiotherapy (26).

Our data together with other studies present in literature suggest that GHD might be secondary to surgery and/or radiotherapy rather than related to OPG itself (19).

In our population rare endocrine disorders like DS and GHH were diagnosed in younger patients. Dienchepalic syndrome has been exceptionally reported in NF1 related OPGs Cavicchiolo et al reported a good outcome of diencephalic syndrome in a 3-years-old boy with NF1 and hypothalamicchiasmatic OPG after chemotherapy (27). The median age of our children with DS was 4.66 years, while in sporadic cases of OPGs usually DS tends to occur in the first year of life. This might be related to the natural history of OPGs, which tend to grow more slowly in patients with NF1 compared to sporadic cases (19). GHH has been mainly described as a transient condition (28,29), and also in our population this endocrine complication spontaneously regressed in one patient, while for the other one treatment was stopped after one year. Of note, both children were very young (3.9 and 4.1 years respectively). Prevalence of this endocrine disease in our population is remarkably lower than in a previous study by Cambiaso et al (1.7 vs 10.9 %) (30), but this latter study was specifically designed to investigate GHH in patients with NF1 and OPGs. However this condition is likely to be underdiagnosed due to its transitory behaviour, hence a careful auxological follow-up is needed to recognize it. In case of GH excess, treatment should be considered monitoring occurrence of systemic effects of GH excess. We wondered whether endocrinopathies associated with OPGs were associated to lesions contiguous with, or directly involving the hypothalamus. Thus we used PLAN classification (also known as modified Dodge classification, MDC) which better describes the involvement of each segments of the optic pathway and allows to highlight the independent involvement of hypothalamus. In our population, tumour location was associated to increased risk of endocrine disorders (table 4), hypothalamic involvement remaining the only predictor in the multivariate analysis, HR 5.82 (2.12-15.93), p=0.001.

Hence, this finding suggests that a thorough auxological and biochemical follow up is mandatory for patients with OPGs involving hypothalamus at diagnosis, regardless of which segment of the optic pathway is involved.

In addition, our study emphasizes that auxological evaluation is imperative in all NF1 children since clinical signs of endocrine disorders might in some cases lead to a diagnosis of OPG (7,31). We also found that patients with hypothalamic involvement received more treatment than patients without: surgery in 7 and chemotherapy in 11 cases. This might depend by the fact that hypothalamic and chiasmatic OPGs often require surgical debulking (32). Another hypothesis , that might be eventually confirmed by dedicated studies, is that tumors which involve the chiasmatic region (MDC2) might be associated to worse OPGs in terms of wider tumors extension, with secondary visual deterioration which is a major criteria for deciding to start chemotherapy.

Finally, young (<5 years) age at OPGs diagnosis represented a further predictor for endocrinopathies development in univariate analysis. This might be linked to the worse prognosis of OPGs in very young children as age at presentation of OPGs has been associated with an increased risk of clinical progression (32).

#### Conclusions

Endocrine disorders were common in patients with NF1 and OPGs before any treatment and might represent a sign of suspicion of an OPG.

In our experience CPP was the most prevalent endocrine disorder while GHD was not common as previously described. DS and GHH, although rare, can occur in patients with NF1 and OPGs, especially in the youngest ones.

Tumour location was the most important predictor of endocrine disorders, particularly hypothalamic involvement. Hence, physicians should bear in mind that patients with OPGs involving the hypothalamic region need a careful auxological follow-up.

**Data availability:** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

#### References

- Johannessen CM, Reczek EE, James MF, Brems H, Legius E, Cichowski K. The NF1 tumor suppressor critically regulates TSC2 and mTOR. *Proc. Natl. Acad. Sci. U. S. A.* 2005;102(24):8573–8.
- Baptiste M, Nasca P, Metzger B, Field N, MacCubbin P, Greenwald P, Armbrustmacher V, Waldman J, Carlton K. Neurofibromatosis and other disorders among children with CNS tumors and their families. *Neurology* 1989;39(4):487–92.
- Sellmer L, Farschtschi S, Marangoni M, Heran MKS, Birch P, Wenzel R, Mautner V-F, Friedman JM. Serial MRIs provide novel insight into natural history of optic pathway gliomas in patients with neurofibromatosis 1. *Orphanet J. Rare Dis.* 2018;13(1):62.

- Piccirilli M, Lenzi J, Delfinis C, Trasimeni G, Salvati M, Raco A. Spontaneous regression of optic pathways gliomas in three patients with neurofibromatosis type I and critical review of the literature. *Childs. Nerv. Syst.* 2006;22(10):1332–7.
- Brzowski AE, Bazan C, Mumma J V., Ryan SG. Spontaneous regression of optic glioma in a patient with neurofibromatosis. *Neurology* 1992;42(3):679–679.
- Perilongo G, Moras P, Carollo C, Battistella A, Clementi M, Laverda A, Murgia A. Spontaneous partial regression of low-grade glioma in children with neurofibromatosis-1: a real possibility. *J. Child Neurol.* 1999;14(6):352–6.
- 7. Listernick R, Charrow J, Greenwald M, Mets M. Natural history of optic pathway tumors in children with neurofibromatosis type 1: A longitudinal study. *J. Pediatr.* 1994;125(1):63–66.
- 8. Leisti EL, Pyhtinen J, Poyhonen M. Spontaneous decrease of a pilocytic astrocytoma in neurofibromatosis type 1. *AJNR. Am. J. Neuroradiol.* 1996;17(9):1691–4.
- Gottschalk S, Tavakolian R, Buske A, Tinschert S, Lehmann R. Spontaneous remission of chiasmatic/hypothalamic masses in neurofibromatosis type 1: report of two cases. *Neuroradiology* 1999;41(3):199–201.
- Taylor T, Jaspan T, Milano G, Gregson R, Parker T, Ritzmann T, Benson C, Walker D,
  PLAN Study Group. Radiological classification of optic pathway gliomas: experience of a modified functional classification system. *Br. J. Radiol.* 2008;81(970):761–6.
- Stokland T, Liu J-F, Ironside JW, Ellison DW, Taylor R, Robinson KJ, Picton S V, Walker DA. A multivariate analysis of factors determining tumor progression in childhood low-grade glioma: a population-based cohort study (CCLG CNS9702). *Neuro. Oncol.* 2010;12(12):1257–68.
- 12. Gnekow AK, Falkenstein F, von Hornstein S, Zwiener I, Berkefeld S, Bison B, Warmuth-Metz M, Driever PH, Soerensen N, Kortmann R-D, Pietsch T, Faldum A. Long-term followup of the multicenter, multidisciplinary treatment study HIT-LGG-1996 for low-grade glioma in children and adolescents of the German Speaking Society of Pediatric Oncology and

Hematology. Neuro. Oncol. 2012;14(10):1265-84.

- Rodriguez FJ, Perry A, Gutmann DH, O'Neill BP, Leonard J, Bryant S, Giannini C. Gliomas in neurofibromatosis type 1: a clinicopathologic study of 100 patients. *J. Neuropathol. Exp. Neurol.* 2008;67(3):240–9.
- Bizzarri C, Bottaro G. Endocrine implications of neurofibromatosis 1 in childhood. *Horm. Res. Paediatr.* 2015;83(4):232–41.
- Cnossen MH, Stam EN, Cooiman LCMG, Simonsz HJ, Stroink H, Oranje AP, Halley DJJ, de Goede-Bolder A, Niermeijer MF, Keizer-Schrama SMPF d. M. Endocrinologic Disorders and Optic Pathway Gliomas in Children With Neurofibromatosis Type 1. *Pediatrics* 1997;100(4):667–670.
- 16. Bruzzi P, Sani I, Albanese A. Reversible Growth Hormone Excess in Two Girls with Neurofibromatosis Type 1 and Optic Pathway Glioma. *Horm. Res. Paediatr.* 2015;84(6):414–422.
- Sani I, Albanese A. Endocrine Long-Term Follow-Up of Children with Neurofibromatosis
  Type 1 and Optic Pathway Glioma. *Horm. Res. Paediatr.* 2017;87(3):179–188.
- Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. *Arch. Neurol.* 1988;45(5):575–8.
- Gan H-W, Phipps K, Aquilina K, Gaze MN, Hayward R, Spoudeas HA. Neuroendocrine Morbidity After Pediatric Optic Gliomas: A Longitudinal Analysis of 166 Children Over 30 Years. J. Clin. Endocrinol. Metab. 2015;100(10):3787–99.
- Poussaint TY, Barnes PD, Nichols K, Anthony DC, Cohen L, Tarbell NJ, Goumnerova L. Diencephalic syndrome: clinical features and imaging findings. *AJNR. Am. J. Neuroradiol.* 1997;18(8):1499–505.
- Hoffmann A, Gebhardt U, Sterkenburg AS, Warmuth-Metz M, Müller HL. Diencephalic syndrome in childhood craniopharyngioma--results of German multicenter studies on 485 long-term survivors of childhood craniopharyngioma. *J. Clin. Endocrinol. Metab.* 2014;99(11):3972–7.

- 22. Brauner R, Trivin C, Zerah M, Souberbielle J-C, Doz F, Kalifa C, Sainte-Rose C. Diencephalic Syndrome due to Hypothalamic Tumor: A Model of the Relationship between Weight and Puberty Onset. *J. Clin. Endocrinol. Metab.* 2006;91(7):2467–2473.
- 23. Habiby R, Silverman B, Listernick R, Charrow J. Precocious puberty in children with neurofibromatosis type 1. *J. Pediatr.* 1995;126(3):364–7.
- 24. Armstrong GT, Conklin HM, Huang S, Srivastava D, Sanford R, Ellison DW, Merchant TE, Hudson MM, Hoehn ME, Robison LL, Gajjar A, Morris EB. Survival and long-term health and cognitive outcomes after low-grade glioma. *Neuro. Oncol.* 2011;13(2):223–34.
- Merchant TE, Conklin HM, Wu S, Lustig RH, Xiong X. Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. *J. Clin. Oncol.* 2009;27(22):3691–7.
- Sklar CA, Antal Z, Chemaitilly W, Cohen LE, Follin C, Meacham LR, Murad MH. Hypothalamic–Pituitary and Growth Disorders in Survivors of Childhood Cancer: An Endocrine Society\* Clinical Practice Guideline. J. Clin. Endocrinol. Metab. 2018;103(8):2761–2784.
- 27. Cavicchiolo ME, Opocher E, Daverio M, Bendini M, Viscardi E, Bisogno G, Perilongo G, Da Dalt L. Diencephalic syndrome as sign of tumor progression in a child with neurofibro-matosis type 1 and optic pathway glioma: a case report. *Childs. Nerv. Syst.*2013;29(10):1941–5.
- Josefson J, Listernick R, Fangusaro JR, Charrow J, Habiby R. Growth hormone excess in children with neurofibromatosis type 1-associated and sporadic optic pathway tumors. *J. Pediatr.* 2011;158(3):433–6.
- 29. Josefson JL, Listernick R, Charrow J, Habiby RL. Growth Hormone Excess in Children with Optic Pathway Tumors Is a Transient Phenomenon. *Horm. Res. Paediatr.* 2016;86(1):35–8.
- 30. Cambiaso P, Galassi S, Palmiero M, Mastronuzzi A, Del Bufalo F, Capolino R, Cacchione A, Buonuomo PS, Gonfiantini M V., Bartuli A, Cappa M, Macchiaiolo M. Growth hormone excess in children with neurofibromatosis type-1 and optic glioma. *Am. J. Med. Genet. Part*

A 2017;173(9):2353–2358.

- 31. Listernick R, Ferner RE, Liu GT, Gutmann DH. Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. *Ann. Neurol.* 2007;61(3):189–98.
- Campen CJ, Gutmann DH. Optic Pathway Gliomas in Neurofibromatosis Type 1. J. Child Neurol. 2018;33(1):73–81.

Figure 1. Kaplan-Mayer survival curves for pre-treatment endocrine event by hypothalamic involvement.

Figure S1. Kaplan-Mayerendocrine event free survival curve.