

Manifestations and Treatment of Adult-onset Symptomatic Optic Pathway Glioma in Neurofibromatosis Type 1

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Abstract. *This report describes the diagnosis and treatment of a 27-year-old patient with neurofibromatosis 1 (NF1) and late progression of a pre-existing optic pathway glioma (OPG) that caused significant reduction in vision. OPG is one of the diagnostic criteria for establishing the diagnosis of NF1. Most common findings of NF1 are café-au-lait spots, axillary and inguinal freckling of the skin, iris hamartoma (Lisch nodules), and tumors of the central nervous system and peripheral nerves. We successfully applied a modified International Society of Paediatric Oncology chemotherapy regimen for low-grade glioma in children with carboplatin dose adjustment according to the area under the plasma drug concentration–time curve calculation. During and after the chemotherapy, a clear improvement of the visual capacity was achieved. Age-adapted chemotherapy for symptomatic adult-onset OPG in patients with NF1 should be considered in individual cases.*

Neurofibromatosis type 1 (NF1) is the most common neurocutaneous disorder. Recklinghausen's neurofibromatosis is the earlier eponymous designation of the disease, von Recklinghausen being the first to provide a complete description of the histological components of this entity (1). NF1 prevalence is about one in 3,000 (2). The disease occurs in all ethnic groups (3). The *NF1* gene was identified on

chromosome 17 (3). Inheritance is autosomal dominant with complete penetrance. However, the phenotype varies considerably. Several key features of the disease affect the integument, such as café-au-lait spots, axillary and inguinal freckling, and iris hamartoma (Lisch nodules). From the fifth year of life, 60-70% of children with NF1 exhibit choroidal abnormalities (4). However, hallmarks of the disease are tumors of peripheral nerves. Plexiform neurofibroma is a characteristic tumor of NF1, which may also affect the orbit (5) and is in principle considered precancerous (2). Despite the preferential manifestation of tumors in the peripheral nervous system, the former term 'peripheral neurofibromatosis' is obsolete because in NF1, relatively large numbers of patients may experience tumors of the central nervous system (2).

Central nervous system tumors in NF1. Pilocytic astrocytoma (PA) is the most common tumor of the central nervous system in patients with NF1 (2). Hudson was the first investigator to describe optic pathway glioma (OPG) as a distinct entity that is clearly distinguishable from other PAs (5-7). OPG may arise in the optic nerve but can also develop anywhere along the optic tract (2). Later, the connection between OPG and neurofibromatosis was revealed (6-8). Recent studies indicate a preference for the female sex (9-11), but this imbalance is not yet sufficiently proven (12). King *et al.* showed that Caucasian children have a much higher prevalence of OPG than children of African American descent (13). However, these ethnic differences are no longer emphasized (14).

The prevalence of OPG in patients with NF1, primarily children, is reported in the literature to be between 9.5 and 25% (15-18). Current estimates of the prevalence of OPG in NF1 suggest that approximately one in five patients develop this

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neoplasm (15). The occurrence of OPG in patients with NF1 is in the vast majority of cases in childhood. In two studies, the mean age at the time of diagnosis was 4.2 years and 5.8 years, respectively (10, 19). In general, the age of manifestation is mostly up to the age of six years, rarely after. The median age at diagnosis for NF1-associated OPG is later than non NF1-associated OPG, however. There are only a few isolated reports, which describe later manifestations in NF1-affected individuals. A study by Lewis *et al.* in 1984 showed that the mean age at diagnosis in the population they observed was 15 years (20). However, this study was performed prior to establishment of National Institute of Health diagnostic criteria on NF1 (2). On the other hand, a more recent study reported the mean age of manifestation was 12.2 years (21). These differences in the age structure of the first diagnosed patients in several studies may be explained both by increased awareness as well as by local diagnostic capacities. Common to all studies is the finding that OPG is a diagnosis of early life in patients with NF1.

If OPG becomes symptomatic, then in the overwhelming majority, the tumor is already symptomatic during this phase of life. However, many tumors remain asymptomatic and require no therapy. Estimates foresee an asymptomatic course in 50% of cases in NF1-affected individuals. OPG can lead to vision loss and proptosis; Dodge stage II or III disease may cause endocrine disturbances such as precocious puberty. Typical diencephalic dystrophy is more common in non-NF1 OPG. The treatment of OPG occurring in those of young age often proves to be most difficult. Treatment philosophy of OPG has changed dramatically in recent decades and was significantly influenced by the drug therapy during childhood.

Chemotherapy. Most non-NF1 PAs harbor a single mutation of the proto-oncogene BRAF leading to BRAF/mitogen-activated protein kinase (MAPK) pathway activation. Similarly in NF1-associated PAs, loss of neurofibromin activates the RAS/RAF/MAPK pathway, thus inhibition of this pathway is being evaluated in current clinical trials.

At present, conventional chemotherapy is the standard measure for inoperable symptomatic or progressive PA both in pediatric NF1 and non-NF1. The frontline non-surgical approach constitutes a combined application of carboplatin and vincristine as established by the International Society of Pediatrics (SIOP) and Children's Oncology Group. The SIOP regimen includes an induction phase of 21 weeks with application of carboplatin $\times 7$ and vincristine $\times 13$, followed by a consolidation phase with cycles of carboplatin every 6 weeks and vincristine (days 1, 7 and 14). The objective response rate to this sequential therapy was higher in NF1-associated OPG compared to non-NF1 OPG. Thus, the NF1 cohort was exempted from randomization in the follow-up trials, *i.e.* combined therapy with thioguanine, procarbazine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) and

vincristine *vs.* standard in Children's Oncology Group (carboplatin and vincristine, or thioguanine, procarbazine, CCNU and vincristine) or intensified induction (carboplatin/vincristine/etoposide) *vs.* standard SIOP therapy (22).

Cumulative vincristine exposure is high following the SIOP regimen, with well-known side-effects particularly in older patients. Carboplatin allergy occurs in a sizable proportion of patients with a need to switch to alternative consolidation depending on the exact regimen given. Weekly vinblastine monotherapy was introduced by the Toronto group (23) and is already being used as a frontline standard by many centers. It will also be one of three randomized arms in the planned LOGGIC trial for standardized visual assessment and treatment indications including children with visual pathway glioma (24), next to the other experimental arm with a MAPK/ERK kinase inhibitor, and to standard carboplatin/vincristine.

Radiotherapy (RT). In most circumstances RT is reserved for subsequent progression after failure of prior systemic therapies. Focal irradiation offers effective second-line non-surgical management in OPG and a wide variety of techniques have evolved. Fractionated highly conformal stereotactic irradiation with photons is being utilized (27), as is particle therapy and radiosurgical approaches such as brachytherapy. All techniques attempt to spare exposure to surrounding risk organs. The advantage of proton therapy is the ability to apply a high dose of radiation to a localized site. The energy drop rate is very rapid, so that surrounding tissue can be spared (25). Depending on location and extent of disease, the accepted age for primary RT has shifted from 8 to beyond 16 years in the SIOP treatment for non-NF1 OPG. In general, irradiation should be avoided in the NF1 cohort (26, 27) because of an increased risk for radiogenic vasculopathy, malignant transformation and neurocognitive complications.

Surgery. Surgical procedures for OPG may be required for immediate debulking and clearance of cerebrospinal fluid obstruction in select cases. Excision of the affected optic nerve to stop progress *via* the chiasm, previously a common approach, is controversial, as retrograde progression of localized anterior disease in non-NF1 OPG is practically not observed (26). Biopsy, when feasible with justifiable operative risk, is only used when clinical images are not characteristic (27). In contrast to pediatrics, the risk group stratification and therapy recommendations for the much rarer adult PAs are less well defined. Small series suggest that resection is best followed by close observation, reserving RT for salvage or for biopsy-only patients (28).

Efficacy of adjuvant chemotherapy has been demonstrated for some adult non-pilocytic low-grade glioma. RTOG 9082 improved outcome with addition of procarbazine, CCNU and

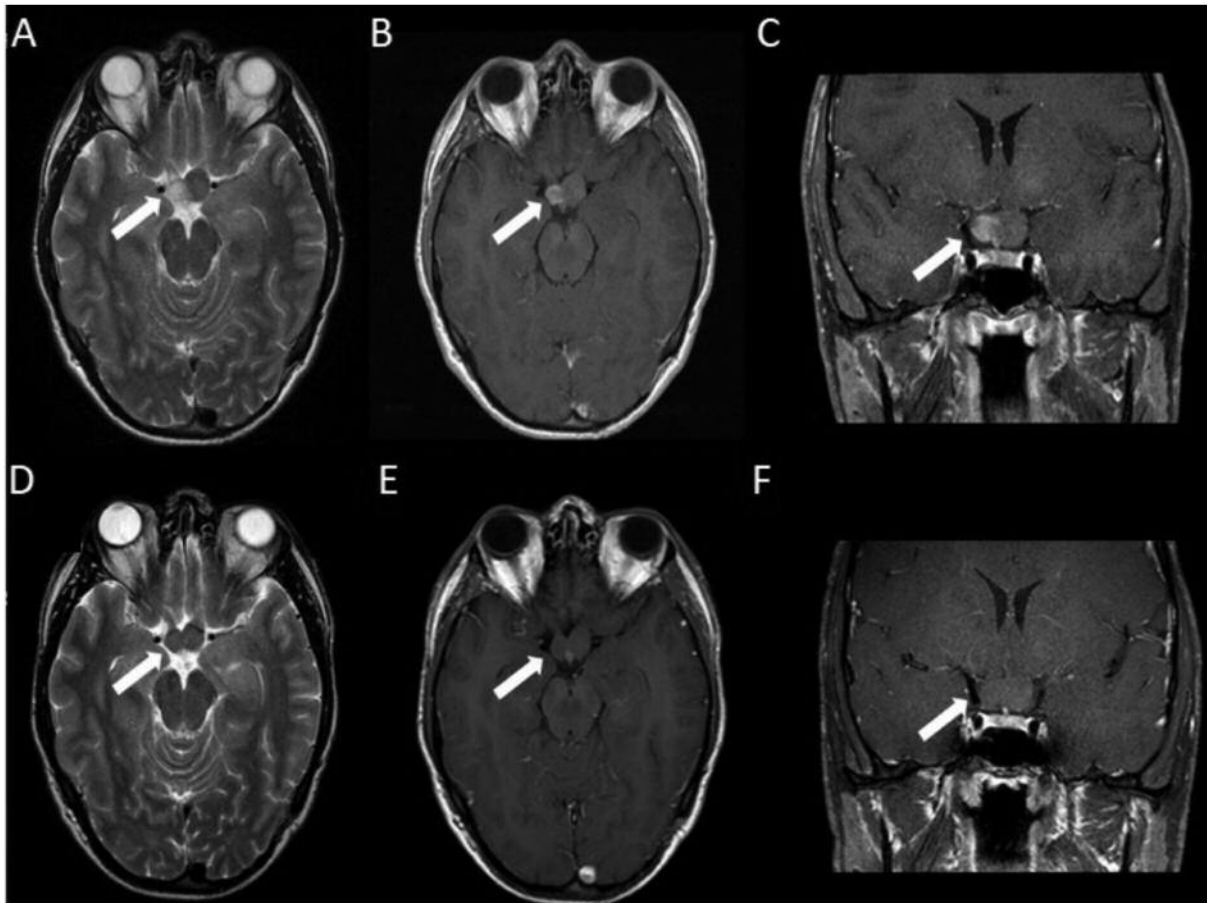


Figure 1. Upper row: Magnetic resonance imaging (MRI) before treatment. A: Axial T2 turbo spin-echo (TSE) sequences showing edema (white arrow) in the chiasma and right proximal optic nerve, as well as tumorous distension of both proximal optic nerves. B: Axial and C: coronal contrast-enhanced T1 TSE MRI showing disturbances of the blood–brain barrier (white arrow) predominantly localized in the chiasma and right proximal optic nerve, with considerable displacement of the pituitary stem. Bottom row: MRI after treatment. D: Axial T2 TSE MRI showing complete decrease of edema (white arrow) and a clear decrease of the space-occupying mass. E: Axial and F: coronal contrast-enhanced T1 TSE MRI showing complete remission of the blood–brain barrier disturbances (white arrow) and no more displacement of the pituitary stem.

vincristine to RT (29) for high-risk adult low-grade glioma, as did a study from University of San Francisco with post-operative temozolomide (30), and more recently, early results from EORTC 22033-26033 showed equivalent progression-free survival in molecularly defined adult low-grade glioma subgroups randomized between dose-dense temozolomide or RT (31). Carboplatin/vincristine experience in adult PA is not on record as far as we are aware.

Case Report

We report the case of a 27-year-old patient with NF1 who was treated with chemotherapy for first symptomatic progression of an optic glioma at the age of 21 years (in 2012). Development delay was present with 1 year, and subsequently

café-au-lait spots, axillary and inguinal freckling led to clinical diagnosis of NF1. Furthermore, delayed motor skills, and dysgrammatism but no other clinical abnormalities were found. Regular magnetic resonance imaging (MRI) surveillance showed focal areas of signal intensity in the *globus pallidus*. Thickening of the left optic chiasm, the left-sided optic tract and the optic nerve were seen on MRI at the age of 15 years. At that time, full visual acuity was preserved, with only some enlargement of the blind spot in the visual field examination. Minimal progression of the OPG was first detected on MRI in 2011. Three years later, further progression was observed, including the right side, in particular the pre-chiasmatic part (Figure 1). Visual acuity of the right (0.5) and the left (0.63) eye was reduced; temporal visual field defects (right: diffuse scotoma, left: absolute scotoma) and reduced visually evoked

Table I. Overview of the chemotherapeutical doses between 6/2014 and 12/2015.

	Time period	Carboplatin (+2 mg vincristine)
Induction phase	25/06/2014 and 26/06/2014	830 mg
	17/07/2014 and 18/07/2014	815 mg
	11/09/2014 and 12/09/2014	830 mg
	08/10/2014 and 09/10/2014	830 mg
	03/11/2014 and 04/11/2014	790 mg
	December 2014	650 mg
Consolidation phase	01/2015-12/2015	650 mg

potentials were diagnosed. These findings prompted the indication for adjuvant chemotherapy (Table I). From June 2014 until December 2014, SIOP induction chemotherapy for low-grade glioma was given modified with carboplatin dose adjusted according to the area under the curve (AUC; 830 mg single dose; dose equivalent to AUC5) and vincristine (2.0 mg single dose). Visual acuity increased to 1.0 on the right and 0.8 on the left in 2015. Continuous regression throughout treatment was observed on subsequent MRI. The patient's visual acuity stabilized. Recovery of the field of vision could not be detected with certainty, however. Following the end of treatment in January 2016, stable disease was seen (Figure 1). Initially therapy was well tolerated, but after week 19, the carboplatin dose was reduced because of nausea and vomiting. Myelotoxicity, peripheral nerve neurotoxicity and ototoxicity were grade 1 or less.

Discussion

OPG in NF1 typically becomes symptomatic during the first decade of life (2, 32, 33). Rarely, as in our case, the pre-symptomatic latent period may be much longer and last into late adolescence or early adulthood, underscoring the need for appropriate long-term ophthalmological surveillance (18). The clinical and pathological characteristics of such patients is different from the cohorts of adult patients with low-grade glioma treated with adjuvant therapy in recent studies (29, 31). Therefore, guidance is probably better extrapolated from the pediatric experience with NF1 and OPG. This report demonstrates that standard pediatric non-targeted chemotherapy with carboplatin and VCR is feasible, effective and well-tolerated after dose adjustment in adults with NF1 and symptomatic OPG.

The described case is instructive as it highlights the risk for late and non-malignant progression of OPG in NF1, with a sustained volumetric and functional response to pediatric-type chemotherapy. This suggests that a late manifestation of OPG in NF1 may be treated with extended childhood therapeutic regimen. Data for long-term outcomes and side-effects from RAS/RAF/MAP/MEK pathway inhibition in

NF1- and non-NF1 OPG will be obtained in future years and will influence our sequential non-surgical treatment paradigms. Until then, it is important to keep in mind that we may resort to the time-tested conventional platin- and vinca-based therapy even in adult NF1-associated OPG.

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