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Treatment of NF1-Associated Optic Pathway/Hypothalamic Gliomas in Patients With Diencephalic Syndrome

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Summary: Diencephalic syndrome is usually associated with tumors in the hypothalamic region, rarely occurring in patients with neurofibromatosis type 1 (NF1)-associated gliomas. We describe the clinical presentation and response to treatment in 3 patients with NF1 presenting with diencephalic syndrome as first symptom of optic pathway/hypothalamic glioma (OPHG). Because of the rarity of this constellation, knowledge about the clinical course and best treatment options for patients with NF1-associated OPHG and diencephalic syndrome is still limited. All 3 patients showed good response to treatment with normalization of body mass index and decrease in tumor volume within 6 months.

Key Words: diencephalic syndrome, optic pathway/hypothalamic gliomas (OPHG), neurofibromatosis type 1 (NF1)

(*J Pediatr Hematol Oncol* 2023;45:e543–e546)

Diencephalic syndrome (DS) is a rare symptom complex associated with tumors in the hypothalamic region, most commonly seen in children with optic pathway/hypothalamic glioma (OPHG).[1] This symptom complex includes weight loss leading to emaciation and can include nystagmus, change in behavior leading to euphoria, and other symptoms.[2] The etiology is unknown even though changes in hypothalamic-pituitary factors involved in appetite regulation and metabolism have been suspected.[3] Different hormonal influences are believed to play a role in DS. Especially growth hormone (GH) is suspected to be a key factor in the development of DS. Elevation of GH, partial resistance to GH, and changes in its regulation have been described in patients with DS.[2,4] Ghrelin and leptin might also play a role but further studies are needed.[3] Although laboratory diagnostic biomarkers are still under investigation, indirect calorimetry has been increasingly used for measuring the hypermetabolic state at diagnosis and monitoring changes in resting energy expenditure during treatment.[5]

Neurofibromatosis type 1 (NF1) is a genetic disorder caused by germline mutations in the *NF1* gene and is associated with predisposition to OPHG and neurofibromas.[6] Children with NF1 usually undergo regular ophthalmological assessments as screening for OPHG.[1,6] NF1-associated OPHGs (detected in 15% to 25% of children with NF1) often show a benign course and may not require any treatment.[6–9]

Indications to start treatment include visual impairment, increase in tumor size over time, or other symptoms associated with the localization of the tumors, such as hydrocephalus or DS. Response to treatment varies and treatment decisions are often challenging, especially in case of potentially life-threatening symptoms, such as DS.[3] So far there are only few cases described of children with NF1-associated OPHG and DS.[5,10–12]

In this report, we present 3 patients with NF1 and DS (Table, Supplemental Digital Content 1, http://links.lww.com/JPHO/A572) who were successfully treated for OPHG, leading to resolution of DS. We highlight the importance of recognizing DS as a rare and potentially life-threatening presentation of OPHGs in children with NF1, which may precede the onset of visual changes.

CASES

Patient 1

A 2-year-old girl with known familial NF1 presented with unexplained weight loss of 2 kg over the past 6 months with crossing of percentiles from normal to a body mass index (BMI) z score of −2.8. Up until then she had been followed because of her NF1 by neurology and dermatology without any remarkable findings. Brain magnetic resonance imaging (MRI) showed a large tumor in the chiasmatic-hypothalamic region, consistent with an OPHG (Fig. 2A).

A central catheter was placed. Because of the tumor extension, young age and possible worse response to treatment, combination therapy with weekly vinblastine and biweekly bevacizumab was started.[13,14] As supportive therapy, a nasogastric tube was inserted for supplementary

Received for publication July 18, 2022; accepted September 14, 2022.
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All included patients and/or parents signed a general research consent of the hospital they were treated in.
Legal guardians of all patients consented in publishing their data.
We received funding for our research from the Palatin Stiftung and from the Stiftung Schwab Seubert.
A.W. and H.H. contributed to data collection, all authors contributed to data analyses. R.K. and P.G. performed radiological assessment and volumetric analyses. A.W. and A.S.G.S. wrote the first draft of the manuscript.
The authors declare no conflict of interest.
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Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.jpho-online.com.

DOI: 10.1097/MPH.0000000000002569

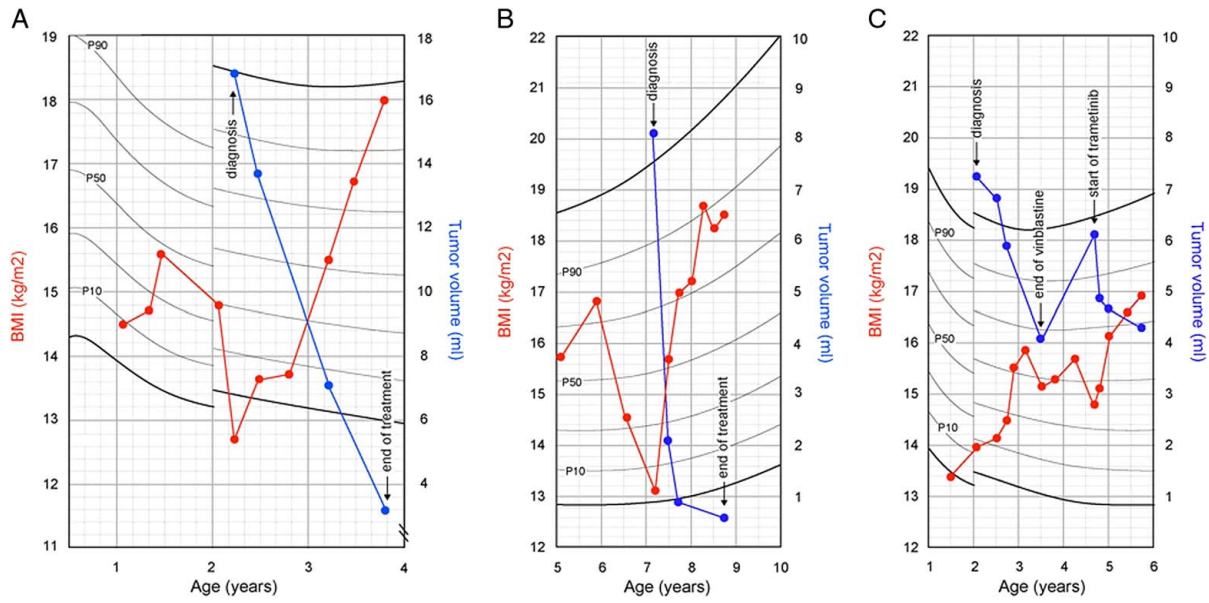

FIGURE 1. BMI (red) and tumor volume (blue) over time. Patient 1 (A), patient 2 (B), patient 3 (C). In gray/black, the age-correlated World Health Organization BMI percentiles/growth curves for girls are highlighted (third to 97th percentile) for comparison in the background. BMI indicates body mass index.

feeding. She rapidly improved, with increasing BMI (z score of −1.7) (Fig. 1A) and tumor reduction (volume at diagnosis: 16.8 mL, at first follow-up: 13.8 mL) on MRI after 2.8 months of treatment (Fig. 2A). After treatment and feeding through the nasogastric tube with high-calorie nutrition for 6 months, the BMI z score increased to −1.5. The tube was removed and food intake was sufficient thereafter. Her BMI at last follow-up at the end of treatment was at a z score of 1.5 (Fig. 1A). Bevacizumab was discontinued after 6 months because of good treatment response, and vinblastine was continued for a total treatment duration of 70 weeks. Tumor volume at the end of treatment was 2.9 mL (Fig. 1A).

Patient 2

A 7-year-old girl with familial NF1 (diagnosed at 6 months of age) presented with failure to thrive. Until then she had been followed by neurology because of her NF1 and showed a normal development. At the age of 2 years, a hypoglossal nerve palsy was suspected but brain MRI was unremarkable. Regular ophthalmology assessments were normal and regular follow-up brain MRIs were deemed unnecessary.

At the age of 7 years and over a period of 4 months, she lost 9 kg and the weight percentile dropped leading to a BMI z score of −1.8 as the length percentile remained within normal range. Celiac disease was ruled out and additional laboratory investigations were noncontributory. As part of the diagnostic workup for weight loss, brain MRI was done because of the known diagnosis of NF1. The MRI showed an OPHG with mild hydrocephalus (Fig. 2B1). The tumor was deemed unresectable and the child was referred to oncology for further treatment.

After placement of a central catheter, chemotherapy with weekly vinblastine was started and well tolerated.[15] With oral nutritional supplements and nutritional counselling, the patient's BMI improved within a few weeks and normalized 6 months after initiation of treatment (BMI z score at first follow-up: −0.1 and after 6 mo: 0.5). The MRI also showed a clear response (Fig. 2B2, B3) to treatment already 3 months after starting chemotherapy with continued decrease in tumor size over time (reduction of tumor volume at diagnosis of 8.1 to 2.1 mL at first and 0.9 mL at second follow-up) (Fig. 1B).

Patient 3

A preterm girl (33 Weeks of gestation), born with normal weight for gestational age, was diagnosed with failure to thrive at 2 months of age. An extensive diagnostic workup, including a gastroscopy, was unremarkable. On the basis of the symptoms, cow's milk protein allergy was suspected and cow's milk protein–free diet was initiated, without relevant improvement. At the age of 11 months genetic testing was done because of multiple café-au-lait spots, muscular hypotonia and dysmorphic features, and diagnosis of sporadic NF1 was made. Persistent failure to thrive, as well as mild developmental delay, in the constellation of known NF1, led to an MRI at the age of 2 years and revealed an OPHG (Fig. 2C1). Visual evoked potentials at the time of OPHG diagnosis were abnormal but the ophthalmological examination was still without any findings of visual impairment. The indication for treatment was given and a central venous catheter inserted. A percutaneous endoscopic gastrostomy for enteral nutritional support was performed. Treatment with vinblastine weekly was started and well tolerated for a total of 70 weeks. The tumor showed partial response to treatment in terms of volume reduction (at diagnosis: 7.3 mL, at end of vinblastine: 4.1 mL) and the patient's weight improved within 6 months with BMI z score increasing from −1.5 to −1.3 and to −0.2 at the end of treatment with vinblastine (Fig. 1C).

The follow-up MRIs after ending vinblastine showed a slow but continued tumor progression so that 1 year after the end of treatment with vinblastine, trametinib was started as a second-line therapy. The patient had no DS symptoms at this time point and her weight remained within normal percentiles and BMI (z score: −0.4) (Fig. 1C). On imaging,

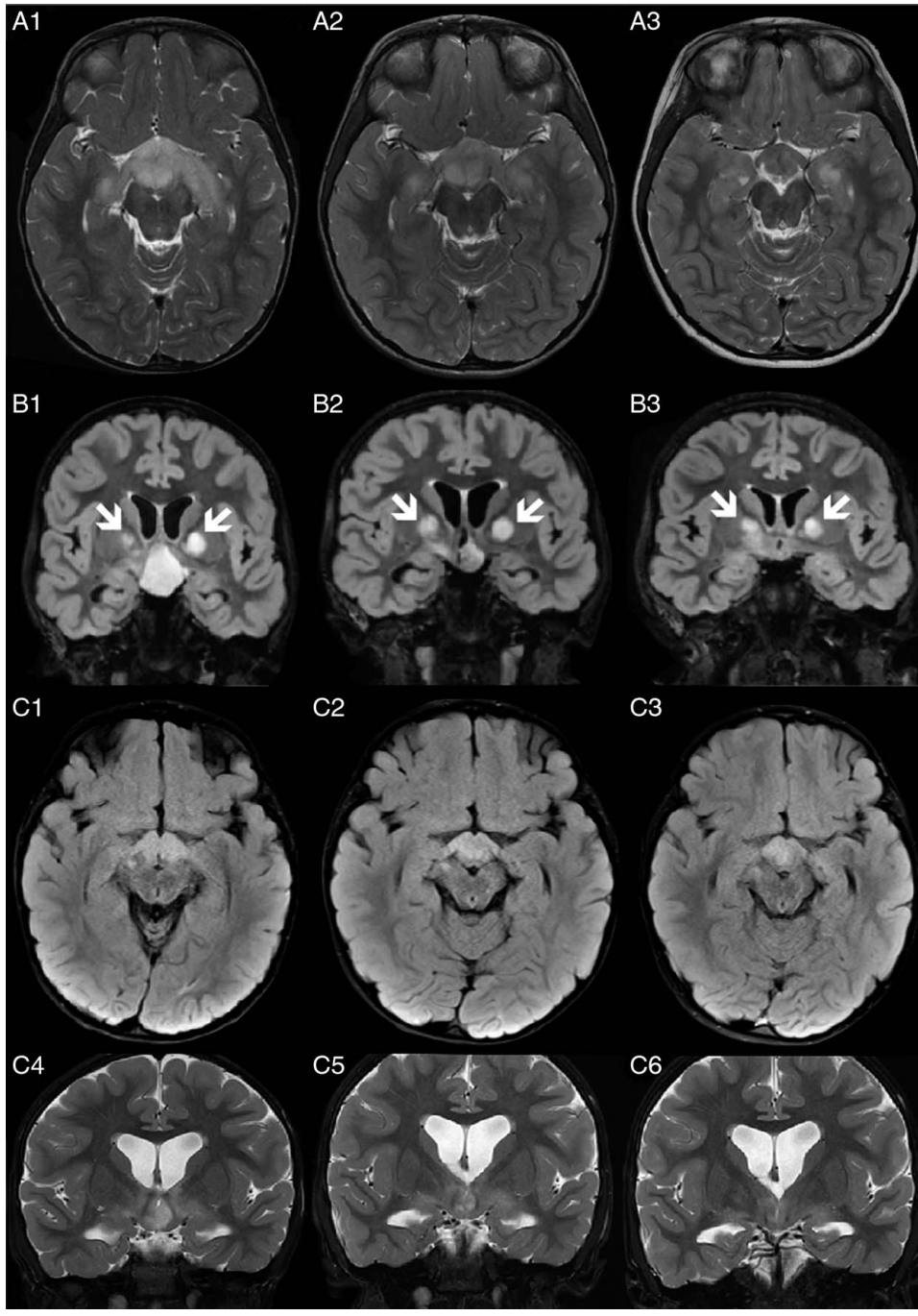

FIGURE 2. Representative magnetic resonance images at diagnosis, at first magnetic resonance imaging follow-up and end of treatment. Patient 1 at diagnosis (A1), 2.8 months after start of VBL and bevacizumab (A2) and at end of treatment (A3); axial T2. Patient 2 at diagnosis (B1), 3.1 months after start of VBL (B2), and at end of treatment (B3); coronal FLAIR. Focal signal hyperintensities specific for NF1 in bilateral globus pallidus (white arrows). Patient 3 at diagnosis (C1), 2.7 months after start of VBL (C2) and at end of treatment (C3); axial T2. Patient 3 at progression (C4), 2.5 months after start of trametinib (C5), and at last follow-up 13.8 months after start of trametinib (C6); coronal T2. FLAIR indicates fluid-attenuated inversion recovery; VBL, vinblastine.

there was a partial response to trametinib, with radiological regression of the hypothalamic tumor already after 3 months (tumor volume at start of trametinib 6.2 mL, after 3 months of treatment 4.9 mL) (Fig. 2C5). Her BMI z score increased and was 0.9 at last follow-up (after 13 months of treatment with trametinib) (Fig. 1C).

DISCUSSION

DS is a rare presentation of OPHG in patients with NF1.[1,10,11,16] In the report on the results of the HIT-LGG 1996 study, 109 patients with NF1-associated OPHG were analyzed. None of these patients presented with DS.[17]

In a retrospective analysis of 520 patients with LGG at SickKids in Toronto, 9 patients with DS were treated with chemotherapy with good treatment response but 7 of them progressed and needed multiple lines of treatment.[5] Two of these 9 patients with DS had NF1 and were treated with chemotherapy. One of the 2 patients progressed multiple times and needed different lines of chemotherapy and surgery. Review of the reported cases of NF1-associated OPHG presenting with DS (Table, Supplemental Digital Content 1, http://links.lww.com/JPHO/A572) shows initial chemotherapy with carboplatin and vincristine was used in most cases,[4,5,10,11] later changed to vinblastine in 3/14 patients.[5,11] Our 3 patients responded well to initial treatment with vinblastine, highlighting this as valuable and potentially less toxic treatment alternative. Also, targeted treatment with trametinib led to treatment response after progression in patient 3.

Diagnosis of OPHG, in patients presenting with DS, is generally made at a younger age, than in patients with other presenting symptoms of OPHG.[3,18] In the analysis of 520 patients with LGG at SickKids, the mean age for patients with OPHG without DS was significantly higher (4.56 y).[5] Previously reported cases of NF1-associated OPHG presenting with DS Table, Supplemental Digital Content 1, http://links.lww.com/JPHO/A572) had a median age at diagnosis of 1.77 (range: 0.5 to 5.8 y).[4,5,10–12,19] One of our patients was already 7 years old at onset of symptoms, which might suggest a different behavior of OPHG and clinical course in patients with NF1 with presentation at an older age. This is also in accordance with other reports in the literature that describe the diagnosis of DS in NF1-associated OPHGs at a later age than DS in sporadic OPHGs.[4,10] The underlying reasons for this different behavior in terms of age at symptom onset are unknown. An association with slower tumor growth in children with NF1 could be one of the reasons.

The most common presenting sign of OPHG is visual impairment. Therefore, children with NF1, who are predisposed for development of OPHG, should undergo regular screening by ophthalmological assessment.[20] Because of the often benign and self-limiting course of NF1-associated OPHG, the presence of visual symptoms is the main indication for treatment.

All our patients developed DS in the absence of visual deterioration or abnormal findings in ophthalmological checkups. Also, in previously reported cases, additional visual symptoms were described in only 5/14 children.[4,5] This highlights the importance of regularly assessing growth and weight in patients with NF1 as an additional screening tool to detect OPHG.

Usually, patients with NF1-associated OPHG have a better prognosis than patients with sporadic OPHG, but patients with OPHG and DS have a worse prognosis compared with patients presenting without DS.[5] As DS can be life-threatening, treatment decisions in these patients are challenging, especially in the rare constellation of NF1-associated OPHG and DS.

Knowledge about DS and early recognition of the symptoms is key to make the diagnosis early and start treatment as soon as possible. It will be helpful to learn more about the treatment decisions by reporting more cases.

ACKNOWLEDGMENTS

The authors thank patients and parents for the consent to publish the data. Furthermore, the authors thank Julia Mühler and Odile Gaisl (Division of Endocrinology of the University Children's Hospital Zurich) for helping with the correct reporting of the anthropometric data. The authors also thank the Palatin Stiftung and the Stiftung Schwab Seubert for funding support.

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