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ORIGINAL ARTICLE

Retrospective analysis of the clinical and radiological features of 94 consecutive DIPGs patients to investigate the factors determining the development of hydrocephalus and its impact on clinical status and survival

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Abstract

Purpose There is no consensus in the literature about the impact of hydrocephalus on clinical course and overall survival of diffuse intrinsic pontine gliomas (DIPG) patients as well as about its specific treatment. Authors reviewed a series of DIPG patients to investigate factors related to the onset of hydrocephalus, its treatment, and its impact on clinical course and prognosis.

Methods A retrospective observational study was performed enrolling pediatric patients affected by DIPG from 2008 to 2018. Clinical and radiological charts were reviewed to find patients' demographic, pathologic and radiologic features in hydrocephalic and non-hydrocephalic patients. In the hydrocephalus cohort, treatment strategy and its effectiveness and complications were analyzed.

Results Ninety-four pediatric patients were enrolled in the study. Patients who developed hydrocephalus showed significantly lesser maximum axial tumor areas than patients without hydrocephalus (respectively 6.5 cm^2 vs 16.45 cm^2, $p < 0.005$). Hydrocephalus developed in 33 patients (35%) with an onset interval of 5.24 ± 1.21 months (range 3.2–7.3). The majority of hydrocephalic patients (28 cases, 90%) were treated by ventriculoperitoneal shunt, the remaining 3 patients being treated by endoscopic third ventriculostomy. Mean overall survival was 16.6 months ± 20 months without significative difference between the groups.

Conclusion The onset of hydrocephalus occurs in the first moths of the disease story and found a negative correlation with tumor maximal axial diameter. Early treatment of hydrocephalus presents a very low complications rate with satisfying clinical outcome, as it allows the patients to continue the neurooncological therapies being a part of the treatment armamentarium instead of a palliative solution.

Keywords Diffuse intrinsic pontine glioma · Hydrocephalus · Endoscopic third ventriculostomy · Ventriculo peritoneal shunt

Introduction

Diffuse intrinsic pontine glioma (DIPG) is a devastating disease accounting for 6–9% of brain tumors in children [1]. The current treatment strategy includes at least focal radiotherapy, but different other medical treatments have been proposed during time [2]. However, these treatments have not achieved sufficient effects on prognosis that remains poor, with a mean survival time of less than 1 year [3, 4], a 12-month overall survival (OS) of 35% [4], and a 2-year OS of less than 20% [3, 5, 6]. Although clinical deterioration of most of patients harboring DIPG is mostly due to progressive brainstem nuclei and long-tracts dysfunction, seldomly, it may be consequent to the development of obstructive triventricular hydrocephalus that can impair the state of consciousness. The rate of occurrence of hydrocephalus in DIPG patients varies among series [7, 8], and there are few data about its correlation with tumor neuroradiological features and changes. The development of hydrocephalus is classically reported to be correlated to the

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terminal stages of the illness [9], and even if easily diagnosed by neuroimaging, its impact on clinical course of patients may be difficultly evaluable given the frequent concomitance of brainstem compression-related neurological deficits, thus, making extremely arduous to differentiate between tumor progression and hydrocephalus. Considering the overlapping of these pathophysiological factors, it has been difficult to find a consensus in the literature about the impact that hydrocephalus and its specific treatment can have on the clinical course of the disease, on the quality of life, and on the overall survival keeping into account the final dismal prognosis that could even suggest an abstention from hydrocephalus treatment. We therefore retrospectively reviewed a series of children with DIPG to investigate the presence of clinical or radiological factors correlated to the onset of hydrocephalus, the modality of treatment, the reasons for specific treatment abstention, or the impact of hydrocephalus management on clinical course and prognosis.

Material and methods

We performed a retrospective observational study enrolling all the patients affected by DIPG diagnosed and treated at the Pediatric Unit of the Fondazione IRCCS Istituto Nazionale dei Tumori (Istituto Nazionale Tumori, INT) from 2008 to 2018. Patients aged 0–21 years were considered as eligible for data collection. The medical ethical committee approved the study (as amendment to clinical protocol INT 153/15). The diagnosis of DIPG was confirmed by neuroradiological review provided by expert radiologists also involved in the SIOPE DIPG Imaging Repository [10]. The following clinical criteria were considered for analysis: demographic features, possible submission to biopsy and percentage of H3K27 gene mutations, development of hydrocephalus and its onset time from the diagnosis, presence of signs and/or symptoms related to hydrocephalus and their differential diagnosis with brainstem and long-tracts deficits, treatment strategy for DIPG, management of hydrocephalus (ventriculoperitoneal shunt—VPS or endoscopic third ventriculostomy—ETV), its efficacy and/or malfunction, rate of ETV intraprocedural abortion and/or postoperative failure requiring conversion to VPS, reasons driving to an abstention from hydrocephalus treatment, possible impact of hydrocephalus treatment on clinical status and on survival.

The following radiological variables were moreover analyzed: diameter and volume of the pontine tumors at the time of diagnosis, sharpened or unsharpened tumor margins, signs of tumor necrosis, edema and/or bleedings, MRI tumor changes at the time of hydrocephalus onset in comparison with tumor features at diagnosis, engorgement of the prepontine cistern by the tumor mass at the time of hydrocephalus onset in view of a potential ETV.

Criteria for the diagnosis of hydrocephalus were as follows: enlargement of temporal horns becoming clearly visible, bowing of third ventricle lateral walls and floor, bundling of cerebral sulci, progressively increasing ventricular volume at the neuroradiologic follow-up ± presence of transependymal resorption, and aggravation of the clinical status (i.e., development of signs and symptoms of intracranial hypertension or the onset/worsening of any kind of neurologic deficits).

According to the development of hydrocephalus, the patient sample was divided into two groups and Fisher's exact test was applied to compare the variables between the two groups. Microsoft Excel (Microsoft Inc.) was used to perform the statistical analysis.

Results

A total of 94 patients were enrolled, with a mean age of 6.29 ± 3.4 years, 57% females and 43% males. Seven patients underwent surgical biopsy (7% of the series): in all cases, H3K27 gene mutated. Specific oncological treatment consisted in focal standard radiotherapy plus nimotuzumab in 37 patients (39%), focal standard radiotherapy plus vinorelbine in 2 patients (2%), focal standard radiotherapy plus nimotuzumab associated with vinorelbine in the remaining patients (55 patients, 58%). The hydrocephalus group consisted of 33 patients (35%), the rest of the cohort not developing hydrocephalus during the course of the disease (61 patients, 65%). No patients had radiologic criteria of hydrocephalus at initial presentation, the mean ± SD interval from the diagnosis of DIPG to the onset of hydrocephalus being of 5.24 ± 1.21 months (range 3.2–7.3). Mean age ± SD in the hydrocephalus cohort was of 6.5 ± 3.5 years, and it did not significantly differ from non-hydrocephalus group (6.22 ± 4.1 years). Clinically, cranial nerve deficits were the most frequent symptom at initial presentation (84 cases, 89%), followed by pyramidal signs (71 cases, 75%), nausea, vomiting, and headache (40 cases, 42%), and finally cerebellar signs (31 patients, 33%). Cranial nerve deficits and nausea, vomiting, and headache resulted to be slightly more frequent in hydrocephalic patients, even if no significant differences between the hydrocephalus and non-hydrocephalus group (Fisher's exact test, $p = 0.12$) (Fig. 1). In hydrocephalus cohort, an unspecific worsening of symptoms led to diagnosis in 89 patients (95%), one patient developed seizures (1%), and finally the remaining 4 patients (4%) did not experience any clinical aggravation (diagnosis performed on progressive ventricular dilatation at systematic MRI follow-up studies). Radiologically, mean maximum axial tumor diameter at the diagnosis was 14 ± 5.6 cm^2, and mean volume was of 23 ± 14 cm^3. Patients who developed hydrocephalus showed significantly lesser maximum axial tumor areas than patients without hydrocephalus (respectively 6.5 cm^2 vs 16.45 cm^2, $p < 0.005$). Tumor margins were unsharped in most of the cases (68

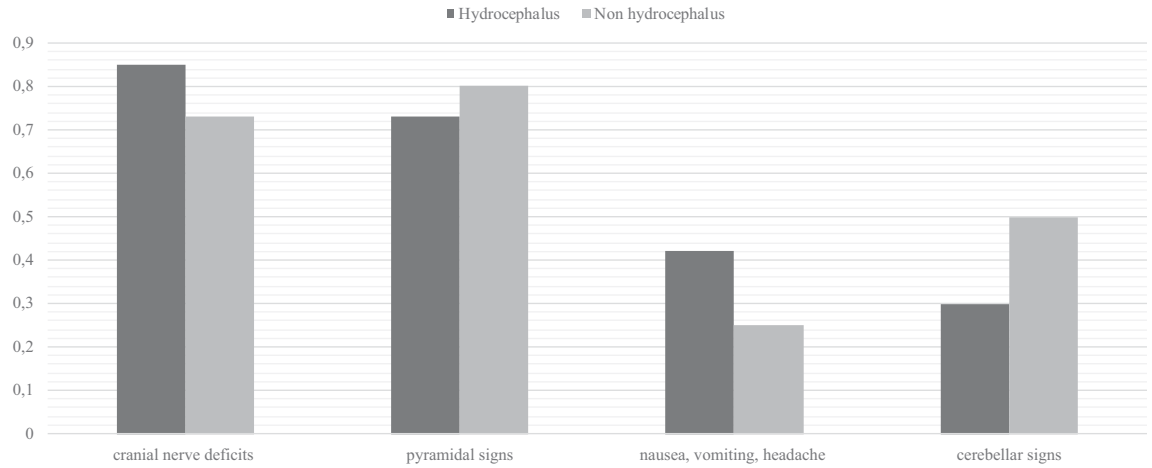

Fig. 1 Signs and symptoms at the diagnosis of the 94 DIPG patients analyzed according the presence of hydrocephalus. No significative differences were found between the groups

patients, 72%), edema was present in 8 patients (9%), necrosis in 59 patients (63%), while intralesional hemorrhage in 17 patients (18%) (Fig. 2). None of these radiological features predicted the onset of hydrocephalus. Treatment of hydrocephalus was envisaged in 31 patients (94% of the hydrocephalus cohort). Two patients were not treated because of very poor clinical conditions with signs of brainstem dysfunction. Twenty-eight (90%) patients were treated with VP shunt, while 3 patients (10%) underwent an ETV. Only 1 shunted patient experienced signs and symptoms of shunt malfunction and required shunt revision. No patients undergoing ETV developed periprocedural complications. One ETV patient required a later conversion to VPS for a failure of the stoma. The treatment of hydrocephalus improved clinical status in all the patients. Mean overall survival (OS) was of 16.6. There was no significant difference between the two groups when Kaplan-Meier log-rank analysis was performed (16.72 months for patients without hydrocephalus, 15.95 patients with hydrocephalus, p value 0.8) (Fig. 3).

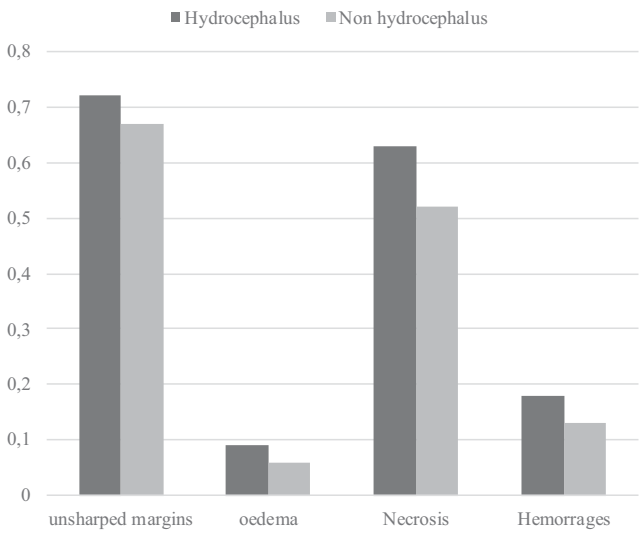

Fig. 2 Mean radiological features at the diagnosis of the tumors analyzed according the presence of hydrocephalus. No significative differences were found between the groups

Discussion

In 2014, Janssens et al. published a clinical study on DIPG patients drawing a survival prediction model [4] that was successively externally validated by Veldhuijzen van Zanten et al. in 2017 [11]. In these studies, patients were reported to frequently develop hydrocephalus (21% and 22%, respectively). Although these are the two largest retrospective studies on DIPG and the incidence of hydrocephalus is not negligible, no factors predicting its development among the many variables analyzed have been investigated. Furthermore, no information about the diagnostic criteria used to define the presence of hydrocephalus or about the specific treatment are reported. In our retrospective study, several clinical and radiological variables were analyzed to better understand hydrocephalus development and its impact. In our series, the diagnosis of DIPG was based on a centralized MRI images review in 93% of the cases because of the presence of typical diagnostic criteria of DIPG [12]. In 7% of patients, a biopsy was required due to uncertainties in radiological diagnosis. All the biopsies confirmed a H3K27 gene mutation. All our DIPG patients underwent homogeneous protocols with a combination of radiotherapy and chemotherapy (nimotuzumab or vinorelbine or a combination of both). In our cohort, 35% of the patients developed hydrocephalus. This data is consistent with the literature where the incidence of hydrocephalus varies between 21 and 89% in the few reported series. Moreover, the mean interval of hydrocephalus onset from the diagnosis of 5.24 ± 1.21 months was similar to the previous reported series (French group 2011 = 5.4 months [8]; Japanese group 2001 = 5.1 [7]), as well as the fact that no patient presented hydrocephalus at the diagnosis (only 1 case

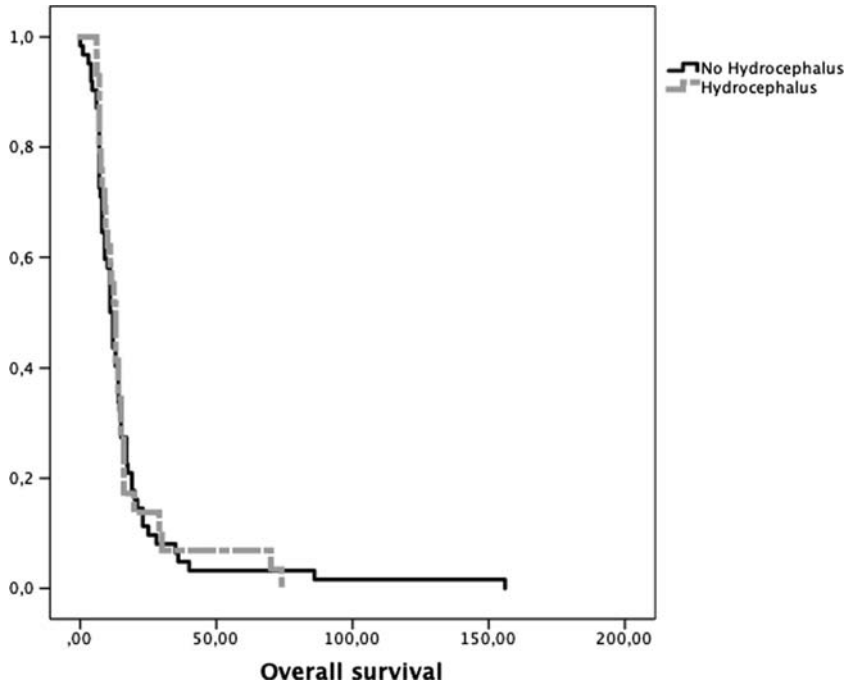

Fig. 3 Kaplan-Meier curve analyzing overall survival of DIPG patients according to the onset of hydrocephalus (black continuous line = hydrocephalic patients; gray interrupted line = nonhydrocephalic patients). No significative differences were found between the groups

in the French paper had signs of hydrocephalus leading to the diagnosis of DIPG). Considering the fact that the mean overall survival was of 16.6 months with no significant difference between the hydrocephalic and non-hydrocephalic groups, the onset of hydrocephalus in DIPG patients is not to be considered as an end stage peculiarity. In this view, the treatment of hydrocephalus does not represent a purely compassionate act but has a relevant role in the management of these patients because it allows continuing the oncological treatment, naturally if its onset does not fall in the terminal stages of the disease. This is the reason why most of the patients in our series developing hydrocephalus were treated, except two patients whose clinical conditions were very poor even before its onset. From the clinical point of view in the present series possible, "preliminary" symptoms leading to hydrocephalus development were difficult to distinguish from general neurological deterioration because none could be in fact specifically attributed as predictive of the hydrocephalus development. The diagnosis of hydrocephalus in our series was therefore mainly confirmed by CT scan or MRI.

Among the radiological features analyzed retrospectively in our patients, only tumor area at the time of diagnosis correlated significantly with the development of hydrocephalus. Surprisingly, patients developing hydrocephalus showed smaller maximum axial tumor areas at the diagnosis. We chose to analyze tumor dimension at the diagnosis because of the significative volumetric decrease of DIPGs during radiotherapy [13]. This data apparently goes against the obstructive physiopathology of hydrocephalus in DIPG tumors. The hydrocephalus described in these patients was always triventricular and determined by an aqueduct obstruction, intuitively possibly due by larger tumors determining an aqueduct involvement. An explanation of the different phenomenon, involving instead "smaller" tumors, could be a correlation with the biological aggressiveness of the tumor. Taking into account that the cohort of symptoms was very variable and overlapping between tumor progression and hydrocephalus, we can infer that smaller tumors induced enough clinical signs and symptoms to reveal a pontine glioma as larger tumor but were maybe biologically more aggressive in comparison with the latter's. From an anatomical point of view the centrifugal and centripetal invasion and disruption of brainstem fibers and nuclei in smaller tumors could determine more rapidly an aqueductal obstruction. Larger tumors could be less aggressive in their pattern of growth allowing an initial compensation of the CSF dynamic and a later hydrocephalus onset. The use of DTI fiber tracking in DIPG tumors at diagnosis could be helpful to verify in the future the consistence of this hypothesis [14, 15]. Poussaint et al. in 2016 published that ADC histogram metrics in DIPG correlate lower diffusion (increased cellularity) and a more aggressive tumor behavior [16]. At the same time, if this hypothesis is correct, we should follow up clinically and radiologically smaller tumors more attentively in order to detect sooner the development of hydrocephalus.

Finally, from the treatment modality point of view, 13% of the hydrocephalic patients that were treated with ETV did not suffer procedural complications and had an acceptable failure rate thereafter requiring a VP shunt. As we previously published [17], ETV is technically feasible, safe, and effective in DIPG patients despite the fact that almost invariably tumor mass infiltrating the pons reduces the volume of interpeduncular and prepontine cisterns available to perform a cisternostomy. In the common practice, at the time of lateral ventricular puncture with

cerebrospinal fluid drainage, surgeons experience a relief of the hydrostatic pressure on the third ventricle floor with its consequent detachment from the cisternal neurovascular structures. The rate (3.6%) of shunt malfunction was very low in the present series underlining that the treatment of hydrocephalus in these patients is due in spite of the dismal final prognosis because of life course amelioration.

Conclusions

In the present retrospective study, one-third of the patients developed hydrocephalus, and it occurred in the first moths of the disease story and not as a final complication. Preliminary symptoms leading to hydrocephalus development were difficult to distinguish from neurological impairment. Radiologically smaller tumors developed more easily hydrocephalus suggesting a different biological aggressiveness of the tumors and possible different follow-up strategies. The treatment of hydrocephalus in the first stages of the disease presented a very low complications rate allowing the patients to obtain a clinical benefit and to continue the neurooncological therapies being a part of the treatment armamentarium instead of a palliative solution. ETV is a surgical option and has to be considered as an alternative to VP shunt.

Compliance with ethical standards

The medical ethical committee approved the study (as amendment to clinical protocol INT 153/15).

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