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ORIGINAL ARTICLE

Desmoplastic infantile astrocytoma and ganglioglioma: a series of 12 patients treated at a single institution

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Abstract

Background Desmoplastic infantile astrocytomas and gangliogliomas (DIA/DIG) usually present with a large size, large cystic component, large dural implant, encasement of big vessels, clinical presentation within 18 months of life, high incidence of seizures and overall good prognosis, even if tumour surgery can be very challenging at first procedure.

Methods We retrospectively reviewed clinical and radiological data of patients diagnosed with desmoplastic infantile tumours who were surgically treated between 2008 and 2019.

Results The series included 12 patients. The median age at surgery was 91 days. The average tumour volume was 212 cm^3. Cystic components were predominant ranging from 0 to 295 cm^3. Active hydrocephalus was pre-operatively evident in 5 cases. Eight patients (66.6%) received total or subtotal removal, three of them (25%) underwent partial removal, and one patient (8.3%) received a biopsy. One patient died within 24 h after surgery due to severe hypotension, as a consequence of significant intraoperative blood loss. Overall, seven (58.3%) patients were reoperated on the tumour after the first procedure: 4 patients were operated twice; 3 patients were operated 3 times. Two patients presented remote localizations and underwent chemotherapy. At last follow-up, 7 patients were tumour-free, 2 are alive with stable disease, and 2 are alive with progressive disease (leptomeningeal seeding).

Conclusion Desmoplastic infantile tumours are rare giant neonatal tumours. Total removal is the goal of treatment, but prognosis remains good even if total removal is not achieved. In case of tumour progression or epilepsy from residual tumour, reoperation is the first option, with chemotherapy reserved to unresectable or disseminated cases with mixed results, while, to date, radiotherapy still plays no role.

Keywords Desmoplastic infantile astrocytoma · Desmoplastic infantile ganglioglioma · Infant · Giant infantile tumour · Cystic tumour · Staged resection

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Introduction

Desmoplastic infantile astrocytomas and gangliogliomas (DIA/DIG) were first described as a distinct entity in the late 1990s [40]. Histology shows divergent astrocytic or astrocytic and ganglionic differentiation, prominent desmoplastic stroma, large size, large cystic component, adhesions to the dura, encasement of big vessels, clinical presentation within 18 months of life and overall good prognosis.

In the 2016 WHO classification of CNS tumours [21], they are classified together as grade I tumours among "neuronal and mixed neuronal-glial tumours", because they share similar clinical, neuroradiological and biological behaviour. DIA/DIGs present a very heterogeneous histological appearance, with areas of high-

grade features that can lead to misdiagnosis. Despite these areas, they usually display a benign clinical course. The main problems in their management are the big volume (often > 5 cm diameter), the encasement of the Willis polygon vessels and the young age of the patients. Many authors suggest radical resection as the treatment of choice, but frequently it cannot be reached, due to the strict adherence to the big vessels and profuse haemorrhage during surgery [23].

We report our experience with twelve patients treated at the Santobono-Pausilipon Children's Hospital. To our knowledge, it is the largest reported single institution clinical series. We discuss multistaged management and prognosis of these tumours, particularly focusing on the destiny and management of residual tumours. In our series, 2 patients with disseminated disease are included.

Materials and methods

All patients with histological diagnosis of desmoplastic infantile tumour that were treated at the Santobono-Pausilipon Children's Hospital (Naples, Italy) were included in this retrospective study. Histological diagnosis was in accordance with the 2016 WHO classification [21]. For patients operated before 2016, histological specimens were reviewed to confirm diagnosis. The study period was 2008–2019. The patients were included only if the entire course of their disease (initial surgery, subsequent treatments and follow-up) was followed by the multidisciplinary team, which included neurosurgeons, oncologists, radiotherapists and neuroradiologists. We retrospectively reviewed case histories and recorded the following data: age at presentation, clinical presentation, radiological features, surgical management, surgical findings, histological results, imaging follow-up and adjuvant therapies. Magnetic resonance (MRI) of the brain and the spine was performed before surgery with gadolinium administration in all cases. All MRI exams were retrospectively reviewed by a neuroradiologist with measurement of the cystic and solid part volumes using a commercially available segmentation software (Horos ®). All surgical procedures were performed using a microsurgical technique. In the last 3 years, IV sodium fluorescein was used to enhance intraoperative recognition of infiltrating tumour areas. All patients received brain MRI within 24 h after surgery to evaluate residual tumour and early post-operative complications. Tumour recurrence was defined by the presence of new pathologic tissue on follow-up MRI. Tumour progression was defined as regrowth of a known post-operative residual.

Results

Clinical presentation

The series included 12 patients (7 females and 5 males) with a sex ratio (female/male) of 1.4. The median age at surgery was 91 days (range, 62–420; mean, 175.16 days). Median follow-up was 72 months (range: 7–132). In 50% of cases, children were referred from the paediatrician for macrocrania (Figs. 1, 2, 3). Two patients (16.6%) presented to the emergency department with new onset of seizures. Numbness and drowsiness were present in 3 patients, associated with hypotonia. Three patients presented hemiparesis. In two cases, the diagnosis was incidental following transfontanellar ultrasound performed to rule out positional plagiocephaly in one patient and an epidermal occipital nodule in the other one.

Radiology

No cases were detected on prenatal ultrasound. Average tumour volume was 212 cm^3 (range: 2.4–444.9 cm^3). Cystic components were predominant, ranging from 0 (1 patient) to 295 cm^3 (average: 161.4 cm^3). Solid component ranged from 2.4 to 166.5 cm^3 (average: 26.2). Active hydrocephalus was evident in 5 cases. Pre-operative MRI showed middle cerebral artery (MCA) encasement in 3 cases before trifurcation, in 2 cases at or after trifurcation. Anterior cerebral artery (ACA) was encased in 1 case. Basilar artery (BA) and/or posterior cerebral artery (PCA) was involved in 2 cases. Major deep draining veins were clearly visible on pre-op MRI in 1 case (patient number 6).

Surgical management and complications

In four patients, the cystic component was responsible for significant intracranial hypertension syndrome and required emergency treatment with insertion of a VAD (ventricular access device) inside the cyst. After patient stabilization, within 6 to 13 days, the tumour was approached with microsurgical technique. In only three (27%) patients, the gross total removal was possible. Five patients (45%) received subtotal removal (removal of > 90% of tumour), two patients received partial removal, and one patient (8,3%) underwent a biopsy. The extent of resection was not related to the initial size of the tumour but rather to the big vessels' encasement. In six cases (50%), the convexity dura mater was infiltrated by tumour and resected during the approach. In one case, the meningeal infiltration was at the tentorium and could not be removed. In the three cases where it was used, IV injection of sodium fluorescein allowed very useful information about tumour boundaries and was considered highly helpful in all cases. Clinically, all patients showed early improvement in their presenting symptoms. Particularly, hemiparesis markedly

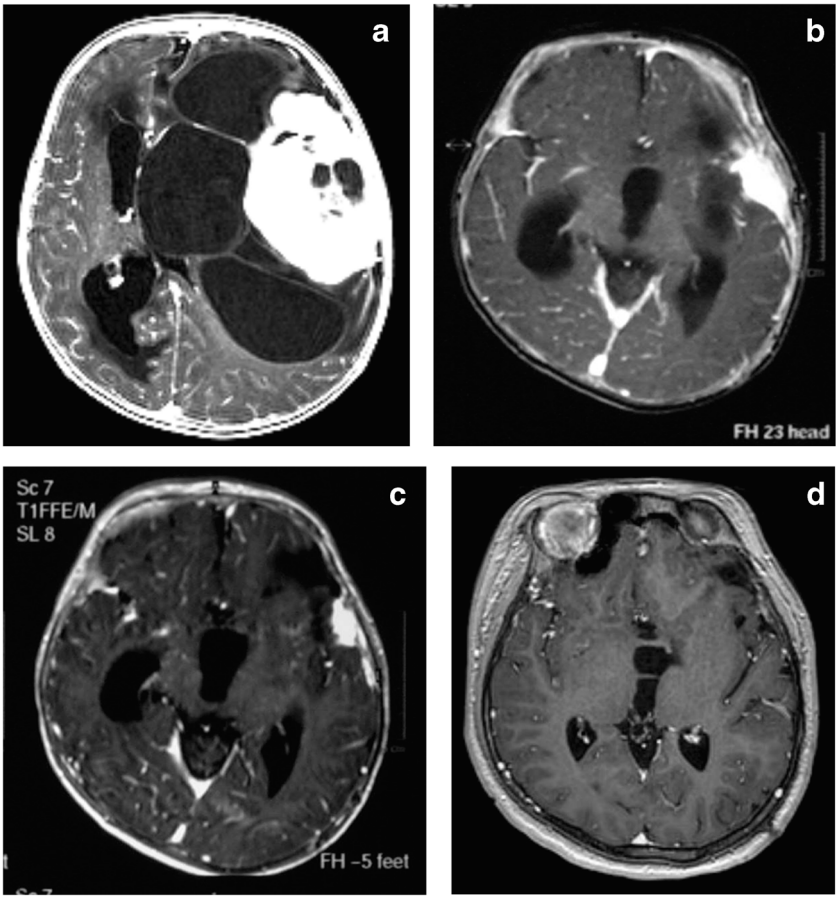

Fig. 1 Case 1: A 4-month-old female presenting with macrocrania, right hemiparesis and poor head control. **a** Axial T1w gadolinium-enhanced MRI showing a left hemispheric tumour with a huge multiloculated cyst associated with active hydrocephalus; subtotal removal of the lesion was achieved because the lesion was tightly adherent to Sylvian vessels. **b** A 6-month follow-up MRI shows a decrease of known residual tumour at the Sylvian fissure. **c** A 1-year follow up MRI shows a further decrease of residual tumour. **d** Last follow-up MRI, 8 years after initial surgery, shows complete disappearance of the tumour: neuropsychological examination revealed normal intelligence (IQt: 90) with no focal neurological deficits

improved in 1 and totally regressed in another patient (the third one is the patient who died in the early post-operative period). Perioperative complications included subdural hygromas in seven patients (58.3%): three of them required implantation of a subduro-peritoneal shunt (all devices were removed after resolution of the hygroma), while conservative management allowed complete resolution in the other 4 cases. Case 11, with a mesencephalic localization and tentorial infiltration, suffered third cranial nerve palsy after second surgery and a paucisymptomatic stroke of the posterior cerebral artery after third surgery. In one case (case 6), surgery was aborted because of severe intraoperative hypotension due to profuse tumour bleeding. Twenty-four hours after surgery, the patient died in the intensive care unit as a consequence of disseminated intravascular coagulation. This patient showed hypertrophic deep tumour venous drainage in pre-operative MRI. In these two cases, the removal was partial.

Seizure management

Only three patients (25%) never experienced seizures during the medical history; in three cases, seizures were the presenting symptom, while 6 patients (50%) presented different forms of epilepsy during the post-operative period that were mainly managed with antiepileptic drugs (AEDs). In two cases, the decision to attempt the microsurgical resection of the tumour recurrence relied on the significant worsening of the epileptic syndrome (become resistant to two AEDs), more than on tumour volume. In one case, surgery allowed long-term seizure control. The second case enjoyed 3-year seizure-free period after tumour resection; then seizures recurred becoming AED resistant: The patient received first a partial hippocampectomy and finally required laser interstitial thermal therapy (LITT). In the remaining four cases, a single AED was able to control seizures.

Destiny of residual tumour

In the three patients in which the removal was complete, tumour did not recur during the follow-up (more than 5 years in all cases). In the five cases with subtotal removal, 1 tumour remained stable (12-year follow-up), and the patient was never reoperated. Two patients had small residuals, not involving vital structures: In these cases, a second surgery was planned and allowed complete removal. In the remaining two patients, residual tumour showed slow progression with worsening of the seizure control. They were reoperated, but again it was not possible to complete removal of the tumour residual.

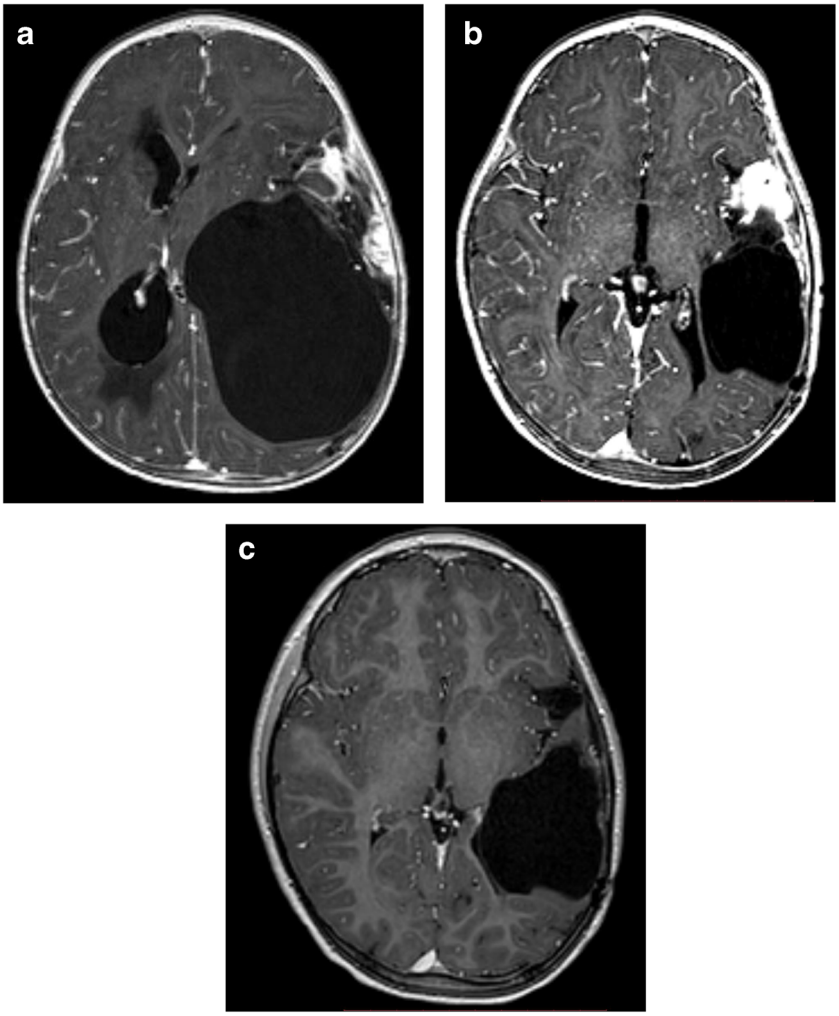

Fig. 2 Case 4: A 13-month-old female presenting with partial seizures, right hemiparesis and severe drowsiness. **a** Axial T1w gadolinium-enhanced MRI showing a very large fronto-temporo-parietal tumour with a peripheral, irregular solid nodule and a massive cyst. **b** A catheter connected with a VAD was placed in emergency in the tumour cyst: the post-operative MRI shows decrease of the cyst volume. The patient underwent tumour microsurgical resection 1 week later: The tumour was tightly adherent to Sylvian vessels, making total removal impossible. The residual nodule increased in size at 3 months, and the girl underwent a new surgical removal. **c** Last follow-up MRI at 32 months shows no residual enhancement, and the girl is completely asymptomatic

Nevertheless, the lesion remained stable over time. One of the two patients with partial removal died in the early post-operative period; the other (with a mesencephalic localization and tentorial infiltration) experienced rapid progression of the tumour and was reoperated 1 month after the first operation. At the second surgery, despite a generous debulking, removal was not satisfactory, because of extensive encasement of the posterior cerebral artery. Chemotherapy with vincristine and carboplatin was started according to SIOP 2004 LGG protocol: The patient experienced slightly reduction of her residual tumour (1-year follow-up).

Metastatic tumour

Two patients presented secondary lesions during the course of their disease: In one patient, the dissemination was evident 3 years after initial diagnosis (biopsy of a small tumoral nodule encasing middle cerebral artery), while in the other case, the diagnosis of the disseminated disease was made at presentation. Surprisingly, both patients presented with a similar lesion arising from the lateral aspect of the midbrain. Both patients were treated according to SIOP 2004 LGG protocol. The response to chemotherapy was heterogeneous. The first patient experienced a very small progression of the perimesencephalic lesion. The lesion slowly progressed despite second-line chemotherapy with bevacizumab and irinotecan. The patient, which is neurologically intact at 6-year follow-up, is under close radiological follow-up: Further treatments (surgery or radiotherapy) will be proposed in case of symptoms manifestation. In the second patient, the solid part remained stable, but a cyst progressed requiring a new craniotomy with microsurgical cyst removal (2 years follow-up).

Follow-up and outcome

Overall, seven (58.3%) patients were reoperated on the tumour after the first procedure: 4 patients were operated twice; 3 patients were operated 3 times. In 3 cases, surgery was prompted by mass progression only and in 2 cases by mass progression associated with AED resistant seizures; in 1 case (case 12, the youngest of the series), the patient received

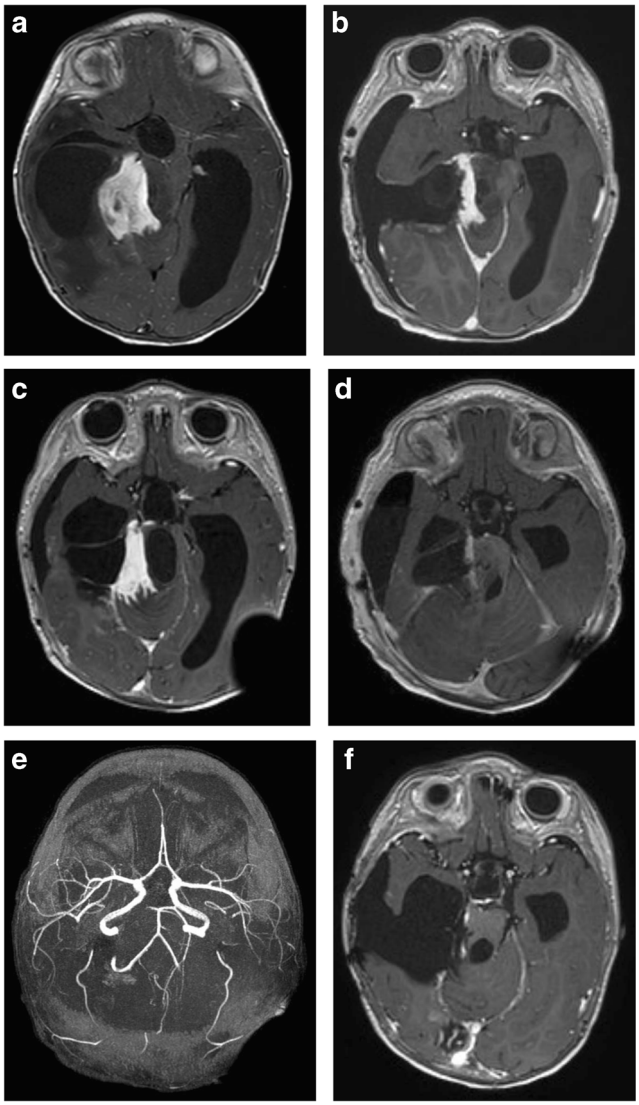

Fig. 3 Case 11: A 8-month-old child, referred to our department because of macrocrania, vomit and irritability. **a** Pre-operative gadolinium-enhanced MRI shows a large tumour with a big cystic component in the right temporal lobe and the solid part tightly adherent to the midbrain, encasing the right posterior cerebral artery. **b** Post-operative MRI performed after removal of the cyst and partial removal of the solid part: The child developed right third cranial nerve palsy. **c** Three months after surgery and two cycles of chemotherapy, MRI shows progression of the solid part: Second surgery was prompted. **d** Second post-operative MRI shows subtotal removal of the residual tumour and an asymptomatic stroke in the territory of the right posterior cerebral artery (**e**). **f** Four months after second surgery, MRI showed significant reduction of tumour residual under chemotherapy for low-grade gliomas (vincristine and carboplatin)

complete resection of the tumour 3 months after partial resection. In 1 case, the patient was reoperated to biopsy a remote lesion in the posterior fossa arising 3 years after biopsy of a temporal lesion. Five patients underwent psychomotor evaluation (the Brunet-Lezine Scale of Psychomotor Development for children from 1 to 30 months of age, and the Wechsler Preschool and Primary Scale of Intelligence test for those from 4 to 6 years of age). Four patients had normal intelligence. One patient presented mild neurodevelopmental delay, with more pronounced speech problems. This patient also presented facial dysmorphism and short stature. He is under endocrinological and genetic evaluation. Regarding motor function, 3/12 patients showed hemiparesis at presentation, of these one patient markedly improved, another showed total recovery, while the third one is the patient who died early in the post-operative period.

Discussion

Desmoplastic infantile tumours (DITs) usually arise in infants in the first 2 years of life [7, 15, 34, 39]; they are large, but history is usually short, suggesting a slow growth rate, until a critical point is reached and becomes symptomatic [7, 23, 25, 34, 36, 39], often at the time of CSF pathway obstruction. The most common presenting symptoms are head enlargement, bulging fontanel and hemiparesis [7, 23, 34]. Delayed development, seizures, skull deformities and symptoms of intracranial hypertension are also common [11].

Surgical treatment is challenging because of the firm texture and vessel and skull base structures involvement. Additional critical points include long surgical time, sudden and/or profuse blood loss with consequent blood transfusions and potential coagulopathy. Because of the above-mentioned features, surgery often results in subtotal or partial removal. The possibility of more than one surgery is always declared to the parents. Need for further surgery can be predicted based on the patient' age (in younger babies, the management is more likely multistage), tumour dimension on pre-operative MRI and big vessels' encasement; however, the final decision to interrupt the operation is taken during the surgery, based on blood loss, hypotension and the anaesthesiologist's opinion. Residual tumour may regrow, potentially triggering drug-resistant epilepsy. Finally, occasional remote localizations can be observed during follow-up and can be difficult to manage due to the intrinsic chemo-resistance of the lesion.

Neuroimaging

Typical neuroimaging features may suggest DIA/DIGs among pre-operative differential diagnosis. This suspicion may be helpful for pathologists at the time of frozen diagnosis and for surgeons to drive the adequate surgical strategy. DIA/DIGs are typically large tumours arising in the supratentorial space mostly located at frontal and parietal lobes [15, 17, 39], often involving more than one lobe [15, 36]. However, the infratentorial location has been also reported, as in one of our cases [24, 38]. They are often composed by a solid portion and a big cyst [3, 25, 34]. The solid portion tends to be peripheral, with leptomeningeal involvement [25, 36, 39], while

the cyst tends to be deeper [3]. Intense contrast enhancement of the solid portion is the most common feature [4, 17, 24, 25, 36]. The cyst walls and septations can be also enhancing [3, 34]. Calcifications are not typical but may be present [4, 17, 36] as well as bone deformities [31, 36]. Surrounding oedema is usually absent or moderate [31, 36] (Table 1).

Histology

DIA/DIGs are characterized by the presence of a prominent, reticulin-rich, desmoplastic stroma, due to the prominent leptomeningeal involvement, and varying proportions of neoplastic neuroepithelial cells [4, 20, 25, 28, 36]. They share all histological features, except for the presence of a neuronal component in DIG [3, 4, 15, 20, 25, 28, 38]. Desmoplasia is defined by increase or modification of connective tissue related to the presence of neoplastic cells with the formation of a collagen rich extracellular matrix [36]. The cellular component is heterogeneous: 3 different neoplastic cell types can be found. The background of the tumour usually consists of streams of spindle astrocytes, usually with slightly swirling or even storiform pattern [20, 36]. Neuronal cells are found only in DIG [3, 15, 20, 25, 28, 34, 36]; they can show variable degrees of maturation [36] and may be sparse or sometimes arranged as clusters. Primitive neuroepithelial cells, with round hyperchromatic nuclei, are present in a small percentage [36]. Calcified deposits are not common but may be present [4]. Mitotic activity, focal hypercellularity and small foci of necrosis are sometimes present, especially in primitive small cell component [4, 17, 23, 34, 36]; all this may lead to misdiagnose as high-grade neoplasms if DIG is not suspected or in case of lack of experience by the pathologist. Immunohistochemical profile of our series, together with the expression of BRAF, did not markedly differ from the previous reports and is resumed in Table 2.

Genetic and molecular profile

Chromosomal alterations in DIA/DIG are rare; recurrent loss at 5ql3.3, 21q22.11 and 10q21.3 were reported; moreover, gain of genomic material at 7q31 (corresponding to MET gene) and at 4q19 has been described [12].

More recently, the mutational status of BRAF has been investigated, and DIA/DIGs harbouring mutations at codon 600 of BRAF gene has been identified, with approximately a 43.8% frequency [41]. Particularly, Wang and colleagues found canonical V600E mutations in 4 histologically DIAs and rare V600D mutations in 3 DIGs.

Surgical planning and management

As reported in many previous papers, DIA/DIGs usually have a benign behaviour; thus, complete surgical excision should be the goal, when possible [7, 8, 11, 23, 32, 33, 36, 39]. When recurrence or regrowth are seen, the treatment of choice is a second surgery [11, 23, 34]. Small biopsy specimens should

Table 1 clinical series. Cases marked by * are those described in the figures

Case	Sex	Age (mths)	Location	Total Tumor Volume (cm3)	Cyst Volume (cm3)	Solid Volume (cm3)	Active hydrocephalus	Emergency cyst drainage	No. Tumor surgeries	Hygroma	SdP shunt	Follow up (mths)	Status
1*	F	4	left FTP	428	295,1	133,2	Yes	-	1	Yes	Yes	132	ANED
2	M	7	right FP	31,8	22,7	9,1	No	-	1	No	No	108	ANED
3	M	8	right PO	182	169,1	12,6	No	-	1	Yes	No	96	ANED
4*	F	14	left FTP	265,9	236,3	29,5	Yes	VAD	2	Yes	Yes	84	ANED
5	M	3	right FTP	228	184,2	43,5	No	VAD	1	Yes	No	108	ANED
6	F	3	right TPO	325,8	159,3	166,5	No	-	1	No	No	-	D
7	M	3	left FTP	444,9	423	22,4	Yes	VAD	2	Yes	No	12	ASD
8	F	3	right FTP	326	272,6	53,8	Yes	-	3	No	No	21	APD
9	M	3	right T	2,4	0	2,4	No	-	2	No	No	84	APD
10	F	11	right FT	126	103,1	22,8	No	-	3	Yes	No	84	ANED
11*	F	8	right TM	428	295,1	22,1	Yes	Ms fenestration	3	Yes	Yes	7	ASD
12	F	2	right FT	95	11,42	83,9	No	-	2	No	No	19	ANED

Legend: F: frontal; T: temporal; P: parietal; O: occipital; M: mesencephalic; VAD: ventricular access device; Ms: microsurgical; SdP: subduroperitoneal; D: Dead; ASD: Alive with Stable Disease; APD: Alive with Progressive Disease; ANED: Alive No Evidence of Disease

Table 2 Immunohistochemical profile of the 12 cases

Case	GFAP	Olig-2	Synaptophysin	NeuN	MAP-2	Vimentin	S100	INI-1	SMA	CD34	P53	Ki67	BRAF V600
1	+		-	-								7%	
2	+		+									8%	
3	+		+	-		+	+			-		7-8%	
4	+		+									7-8%	
5	+		+	-		+	+			-	+	5%	
6	+		+		+	+	+	+			+	3- 20%	
7	+	+	+		+	+	+	+	+	-	+	5-7%	NEG
8	+		+	+	+		+	+	-		+	2-10%	NEG
9	+	+						+		-	+	5-10%	NEG
10	+		+	+	+	+	+				+	1%	
11	+		+			+	+				-	5%	NEG
12	+		+	+/-				+		-	-	7%	NEG

Legend: GFAP: Glial Fibrillary Acidic Protein; Olig-2: Oligodendrocyte Transcription Factor: NeuN: Neuronal Nuclei; MAP-2: MicroTubule Associated Protein 2; S100: S100 Protein; INI-1: Integrase Interactor 1; SMA: Smooth Muscle Actin; CD34: CD34 transmembranous Protein; P53: P53 Tumor Protein; Ki67: Proliferation Index; BRAF V600: BRAF gene mutation

be carefully evaluated as they can be misdiagnosed as malignant tumours and thus be inappropriately treated [23, 32].

Giant cyst management through VAD implant was very helpful in our hands for rapid improvement of critical conditions on admission and to plan the microsurgical procedure as elective surgery. Although radical resection should be considered as the gold standard of treatment, it can be impossible due to two main reasons: giant size with consequent extreme blood loss and big vessels' encasement. Nevertheless, the surgeon must be aware that incomplete removal does not affect the final prognosis: residual tumour usually presents indolent behaviour, can remain stable for years without adjuvant treatment or even disappear completely during follow-up. In case of regrowth, cyst enlargement or modification of seizures pattern, the patient can be reoperated usually obtaining significant further reduction of tumour volume, excellent cyst control and effective long-term control of seizures. For these reasons, it is of outmost importance to suspect this rare histology at the time of presentation and before the first attempt of surgical removal. Surgical strategy, like in all giant tumours of the newborn, should be aimed at maximum safe resection and delayed control (surgical or adjuvant treatment) of the tumour residual. In our hands, reoperation was performed in 7 cases. It was usually much easier than the first procedure; small residuals were easily detected in the depth of large surgical cavities, and IV sodium fluorescein proved highly effective in identification of tumour tissue making radical removal easier. In only one case, a significant complication occurred during reoperations (case 11) resulting in third cranial nerve palsy after second surgery and PCA stroke after third surgery. Third nerve palsy is slowly recovering, and the child is developing well otherwise 7 months after last surgery.

Adjuvant therapy

Most reports agree in an excellent prognosis after total resection; even in case of partial removal, these tumours seem to show a good behaviour [27, 34, 36, 37]; there are also some reports of spontaneous regression after subtotal resection [33, 34]. According to this evidence, there is no further treatment after total removal, and only a close follow-up in partially resected lesions is recommended [3, 4, 7, 19, 27, 34, 37]. In spite of a general good prognosis, metastases, dissemination and rapid progression of residual lesions have been reported [9, 24, 35, 38]. The role of adjuvant therapy in DIA/DIG is still debated, and a well-established protocol is lacking [2, 37]. However, there is an increasing trend to start chemotherapy in cases of tumour progression after surgery with no further surgical resection feasible [11, 24, 26, 27]. The commonest association is vincristine-carboplatin according to the Low-Grade Glioma Protocol of the International Society of Paediatric Oncology (SIOP) [9, 24]; however, consensus has not been reached so far [1, 38], and temozolomide exists as an alternative in case of poor response to the previous therapies (27). The recent discovery of MAPK pathway activation in DIA DIG mainly in the form of BRAF alterations (V600E/D mutations, FXR1-BRAF fusion) indicates that DIA/DIG may represent another MAPK pathway-driven neuroepithelial tumour, similar to pilocytic astrocytoma [6, 16, 18]. These findings expand treatment options when gross total resection is not possible, in case of recurrence, or in case of rare leptomeningeal dissemination or progression of the disease after standard adjuvant therapy [14]. Examples of DIA/DIG with progressive disease that could potentially respond to a

targeted therapy, with selective BRAF inhibitors like vemurafenib, (if a BRAF mutation is demonstrated), are reported [5, 13], but their use is still debatable [1].

Three patients in our series required adjuvant chemotherapy: Two of them presented early dissemination and received a combination of vincristine-carboplatin. The third patient had an infratentorial location in which total removal was judged not achievable; moreover, the patient presented rapid progression of the residual tumour.

Although there are some reports of adjuvant radiotherapy (5, 11, 16), its use seems to have considerably declined during the last decades [10]. Some authors claim the risk for malignancies after such treatment [22, 29, 30].

Conclusions

Desmoplastic infantile tumours are a rare entity that should be early suspected in the clinical course of giant neonatal tumours for a correct management. Total removal is the goal of treatment, but surgery can be challenging, carrying the risk of severe complications. Prognosis remains good even if total removal is not achieved; thus, aggressive surgery is not advisable to reduce the risk of death or major neurological deficits. In case of progression, reoperation is the first option, with chemotherapy reserved to unresectable cases, while radiotherapy to date still plays no role.

Declarations

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Comitato Etico Cardarelli-Santobono) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this retrospective study, formal consent is not required.

References

1. Abuharbid G, Esmaeilzadeh M, Hartmann C, Hermann EJ, Krauss JK (2015) Desmoplastic infantile astrocytoma with multiple intracranial and intraspinal localizations at presentation. Childs Nerv Syst 31:959–964. https://doi.org/10.1007/s00381-015-2715-5
2. Bächli H, Avoledo P, Gratzl O, Tolnay M (2003) Therapeutic strategies and management of desmoplastic infantile ganglioglioma: two case reports and literature overview. Childs Nerv Syst 19:359–366. https://doi.org/10.1007/s00381-003-0754-9
3. Beppu T, Sato Y, Uesugi N, Kuzu Y, Ogasawara K, Ogawa A (2008) Desmoplastic infantile astrocytoma and characteristics of the accompanying cyst. Case report J Neurosurg Pediatr 1:148–151. https://doi.org/10.3171/PED/2008/1/2/148
4. Bhardwaj M, Sharma A, Pal HK (2006) Desmoplastic infantile ganglioglioma with calcification. Neuropathology 26:318–322. https://doi.org/10.1111/j.1440-1789.2006.00684.x
5. Blessing MM, Blackburn PR, Balcom JR, Krishnan C, Harrod VL, Zimmermann MT, Barr Fritcher EG, Zysk CD, Jackson RA, Nair AA, Jenkins RB, Halling KC, Kipp BR, Ida CM (2018) Novel BRAF alteration in desmoplastic infantile ganglioglioma with response to targeted therapy. Acta Neuropathol Commun 6:118. https://doi.org/10.1186/s40478-018-0622-1
6. Blessing MM, Blackburn PR, Krishnan C, Harrod VL, Barr Fritcher EG, Zysk CD, Jackson RA, Milosevic D, Nair AA, Davila JI, Balcom JR, Jenkins RB, Halling KC, Kipp BR, Nageswara Rao AA, Laack NN, Daniels DJ, Macon WR, Ida CM (2019) Desmoplastic infantile ganglioglioma: a MAPK pathway-driven and microglia/macrophage-rich neuroepithelial tumor. J Neuropathol Exp Neurol 78:1011–1021. https://doi.org/10.1093/jnen/nlz086
7. Blount J (2006) Desmoplastic infantile gangliogliomas in: Neuro-oncology of CNS tumors, Springer-Verlag. Tonn, JC; Westphal, JT; Grossman SA, Berlin Heidelberg
8. Chacko G, Chandi SM, Chandy MJ (1995) Desmoplastic low grade astrocytoma: a case report and review of literature. Clin Neurol Neurosurg 97:32–35. https://doi.org/10.1016/0303-8467(94)00051-7
9. Darwish B, Arbuckle S, Kellie S, Besser M, Chaseling R (2007) Desmoplastic infantile ganglioglioma/astrocytoma with cerebrospinal metastasis. J Clin Neurosci 14:498–501. https://doi.org/10.1016/j.jocn.2006.01.024
10. Dudley RWR, Torok MR, Gallegos DR, Mulcahy-Levy JM, Hoffman LM, Liu AK, Handler MH, Hankinson TC (2015) Pediatric low-grade ganglioglioma: epidemiology, treatments, and outcome analysis on 348 children from the surveillance, epidemiology, and end results database. Neurosurgery 76:313–319; discussion 319; quiz 319–320. https://doi.org/10.1227/NEU.0000000000000619
11. Gelabert-Gonzalez M, Serramito-García R, Arcos-Algaba A (2010) Desmoplastic infantile and non-infantile ganglioglioma. Review of the literature. Neurosurg Rev 34:151–158. https://doi.org/10.1007/s10143-010-0303-4
12. Gessi M, Zur Mühlen A, Hammes J, Waha A, Denkhaus D, Pietsch T (2013) Genome-wide DNA copy number analysis of desmoplastic infantile astrocytomas and desmoplastic infantile gangliogliomas. J Neuropathol Exp Neurol 72:807–815. https://doi.org/10.1097/NEN.0b013e3182a033a0
13. Greer A, Foreman NK, Donson A, Davies KD, Kleinschmidt-DeMasters BK (2017) Desmoplastic infantile astrocytoma/ganglioglioma with rare BRAF V600D mutation. Pediatr Blood Cancer 64. https://doi.org/10.1002/pbc.26350
14. Hummel TR, Miles L, Mangano FT, Jones BV, Geller JI (2012) Clinical heterogeneity of desmoplastic infantile ganglioglioma: a case series and literature review. J Pediatr Hematol Oncol 34:e232–e236. https://doi.org/10.1097/MPH.0b013e3182580330
15. Izban KF, Thomas C (1998) Desmoplastic infantile ganglioglioma. Pediatric Pathology & Molecular Medicine 18:157–172. https://doi.org/10.1080/15513819809168784
16. Jones DTW, Hutter B, Jäger N, Korshunov A, Kool M, Warnatz H-J, Zichner T, Lambert SR, Ryzhova M, Quang DAK, Fontebasso AM, Stütz AM, Hutter S, Zuckermann M, Sturm D, Gronych J, Lasitschka B, Schmidt S, Seker-Cin H, Witt H, Sultan M, Ralser M, Northcott PA, Hovestadt V, Bender S, Pfaff E, Stark S, Faury D,

Schwartzentruber J, Majewski J, Weber UD, Zapatka M, Raeder B, Schlesner M, Worth CL, Bartholomae CC, von Kalle C, Imbusch CD, Radomski S, Lawerenz C, van Sluis P, Koster J, Volckmann R, Versteeg R, Lehrach H, Monoranu C, Winkler B, Unterberg A, Herold-Mende C, Milde T, Kulozik AE, Ebinger M, Schuhmann MU, Cho Y-J, Pomeroy SL, von Deimling A, Witt O, Taylor MD, Wolf S, Karajannis MA, Eberhart CG, Scheurlen W, Hasselblatt M, Ligon KL, Kieran MW, Korbel JO, Yaspo M-L, Brors B, Felsberg J, Reifenberger G, Collins VP, Jabado N, Eils R, Lichter P, Pfister SM, International Cancer Genome Consortium PedBrain Tumor Project (2013) Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma. Nat Genet 45:927–932. https://doi.org/10.1038/ng.2682

17. Kim J-H, Kim I-O, Kim WS, Kim KH, Park CM, Yeon K-M (2003) MR findings of desmoplastic cerebral astrocytoma of infancy. Acta Radiol 44:688–690. https://doi.org/10.1046/j.1600-0455.2003.00145.x
18. Koelsche C, Sahm F, Paulus W, Mittelbronn M, Giangaspero F, Antonelli M, Meyer J, Lasitschka F, von Deimling A, Reuss D (2014) BRAF V600E expression and distribution in desmoplastic infantile astrocytoma/ganglioglioma. Neuropathol Appl Neurobiol 40:337–344. https://doi.org/10.1111/nan.12072
19. Lönnrot K, Terho M, Kähärä V, Haapasalo H, Helén P (2007) Desmoplastic infantile ganglioglioma: novel aspects in clinical presentation and genetics. Surg Neurol 68:304–308; discussion 308. https://doi.org/10.1016/j.surneu.2006.11.043
20. Louis DN, von Deimling A, Dickersin GR, Dooling EC, Seizinger BR (1992) Desmoplastic cerebral astrocytomas of infancy: a histopathologic, immunohistochemical, ultrastructural, and molecular genetic study. Hum Pathol 23:1402–1409. https://doi.org/10.1016/0046-8177(92)90061-7
21. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW (2016) The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 131:803–820. https://doi.org/10.1007/s00401-016-1545-1
22. Lundar T, Due-Tønnessen BJ, Fric R, Egge A, Krossnes B, Due-Tønnessen P, Stensvold E, Brandal P (2018) Neurosurgical treatment of gangliogliomas in children and adolescents: long-term follow-up of a single-institution series of 32 patients. Acta Neurochir 160:1207–1214. https://doi.org/10.1007/s00701-018-3550-8
23. Mallucci C, Lellouch-Tubiana A, Salazar C, Cinalli G, Renier D, Sainte-Rose C, Pierre-Kahn A, Zerah M (2000) The management of desmoplastic neuroepithelial tumours in childhood. Childs Nerv Syst 16:8–14. https://doi.org/10.1007/PL00007280
24. Milanaccio C, Nozza P, Ravegnani M, Rossi A, Raso A, Gambini C, Garrè ML, Pietsch T (2005) Cervico-medullary desmoplastic infantile ganglioglioma: an unusual case with diffuse leptomeningeal dissemination at diagnosis. Pediatr Blood Cancer 45:986–990. https://doi.org/10.1002/pbc.20325
25. Nikas I, Anagnostara A, Theophanopoulou M, Stefanaki K, Michail A, Hadjigeorgi C (2004) Desmoplastic infantile ganglioglioma: MRI and histological findings case report. Neuroradiology 46:1039–1043. https://doi.org/10.1007/s00234-004-1283-2
26. Osborn AG, Salzman KL, Jhaveri MD, Barkovich AJ (2015) Desmoplastic infantile astrocytoma and ganglioglioma in: diagnostic imaging: Brain E-Book. Elsevier Health Sciences
27. Pommepuy I, Delage-Corre M, Moreau JJ, Labrousse F (2006) A report of a desmoplastic ganglioglioma in a 12-year-old girl with review of the literature. J Neuro-Oncol 76:271–275. https://doi.org/10.1007/s11060-005-6500-2
28. Rout P, Santosh V, Mahadevan A, Kolluri VRS, Yasha TC, Shankar SK (2002) Desmoplastic infantile ganglioglioma–clinicopathological and immunohistochemical study of four cases. Childs Nerv Syst 18:463–467. https://doi.org/10.1007/s00381-002-0610-3
29. Rumana CS, Valadka AB (1998) Radiation therapy and malignant degeneration of benign supratentorial gangliogliomas. Neurosurgery 42:1038–1043. https://doi.org/10.1097/00006123-199805000-00049
30. Rumana CS, Valadka AB, Contant CF (1999) Prognostic factors in supratentorial ganglioglioma. Acta Neurochir 141:63–68; discussion 68-69. https://doi.org/10.1007/s007010050267
31. Santhosh K, Kesavadas C, Radhakrishnan VV, Abraham M, Gupta AK (2008) Multifocal desmoplastic noninfantile astrocytoma. J Neuroradiol 35:286–291. https://doi.org/10.1016/j.neurad.2008.04.003
32. Sugiyama K, Arita K, Shima T, Nakaoka M, Matsuoka T, Taniguchi E, Okamura T, Yamasaki H, Kajiwara Y, Kurisu K (2002) Good clinical course in infants with desmoplastic cerebral neuroepithelial tumor treated by surgery alone. J Neuro-Oncol 59:63–69. https://doi.org/10.1023/a:1016309813752
33. Takeshima H, Kawahara Y, Hirano H, Obara S, Niiro M, Kuratsu J (2003) Postoperative regression of desmoplastic infantile gangliogliomas: report of two cases. Neurosurgery 53:979–983; discussion 983-984. https://doi.org/10.1227/01.neu.0000084165.60662.6d
34. Tamburrini G, Colosimo C, Giangaspero F, Riccardi R, Di Rocco C (2003) Desmoplastic infantile ganglioglioma. Childs Nerv Syst 19:292–297. https://doi.org/10.1007/s00381-003-0743-z
35. Taranath A, Lam A, Wong CKF (2005) Desmoplastic infantile ganglioglioma: a questionably benign tumour. Australas Radiol 49:433–437. https://doi.org/10.1111/j.1440-1673.2005.01479.x
36. Trehan G, Bruge H, Vinchon M, Khalil C, Ruchoux MM, Dhellemmes P, Ares GS (2004) MR imaging in the diagnosis of desmoplastic infantile tumor: retrospective study of six cases. AJNR Am J Neuroradiol 25:1028–1033
37. Ulu MO, Tanriöver N, Biçeroğlu H, Oz B, Canbaz B (2008) A case report: a noninfantile desmoplastic astrocytoma. Turk Neurosurg 18:42–46
38. Uro-Coste E, Ssi-Yan-Kai G, Guilbeau-Frugier C, Boetto S, Bertozzi AI, Sevely A, Lolmede K, Delisle MB (2010) Desmoplastic infantile astrocytoma with benign histological phenotype and multiple intracranial localizations at presentation. J Neuro-Oncol 98:143–149. https://doi.org/10.1007/s11060-009-0075-2
39. VandenBerg SR (1993) Desmoplastic infantile ganglioglioma and desmoplastic cerebral astrocytoma of infancy. Brain Pathol 3:275–281. https://doi.org/10.1111/j.1750-3639.1993.tb00754.x
40. VandenBerg SR, May EE, Rubinstein LJ, Herman MM, Perentes E, Vinores SA, Collins VP, Park TS (1987) Desmoplastic supratentorial neuroepithelial tumors of infancy with divergent differentiation potential ("desmoplastic infantile gangliogliomas"). Report on 11 cases of a distinctive embryonal tumor with favorable prognosis. J Neurosurg 66:58–71. https://doi.org/10.3171/jns.1987.66.1.0058
41. Wang AC, Jones DTW, Abecassis IJ, Cole BL, Leary SES, Lockwood CM, Chavez L, Capper D, Korshunov A, Fallah A, Wang S, Ene C, Olson JM, Geyer JR, Holland EC, Lee A, Ellenbogen RG, Ojemann JG (2018) Desmoplastic infantile ganglioglioma/astrocytoma (DIG/DIA) are distinct entities with frequent BRAFV600 mutations. Mol Cancer Res 16:1491–1498. https://doi.org/10.1158/1541-7786.MCR-17-0507