Abstract

Background and Purpose: The 5th edition of the WHO classification of CNS tumors defines new embryonal tumor types, including CNS neuroblastoma with forkhead box R2 (CNS NB-*FOXR2*) activation. Published clinical outcomes are limited but tend to suggest a favourable outcome after surgical resection and adjuvant therapy. This multi-center study aims to describe imaging features of CNS NB-*FOXR2*, poorly characterized thus far.

Materials and Methods: Based on a previously published cohort on tumors molecularly classified as CNS NB-*FOXR2*, patients with available imaging data were identified. The imaging features on preoperative MRI and CT data were recorded by eight experienced pediatric (neuro)radiologists in consensus review meetings.

Results: Twenty-five patients were evaluated (13 females; median age 4.5 years). The majority of tumors were large (mean 115 ± SD 83 ml), showed no (24%) or limited (60%) perifocal edema, demonstrated heterogeneous enhancement, were often calcified and/or hemorrhagic (52%), were always T2w hyperintense to gray matter, and commonly had cystic and/or necrotic components (96%). The mean ADC values were relatively low (mean 687.8 10^{-6}mm^2/s ± SD 136.3). The tumors were always supratentorial and never centered in the midline. Metastases were infrequent (20%) and when present, of nodular appearance.

Conclusions: In our cohort, CNS NB-FOXR2 tumors were often very large, exclusively supratentorial, and often in the frontal and parietal lobes with or without involving the deep grey matter. The results of this study may assist in considering this diagnosis preoperatively. Collaborative pooling of cases is important to gain insight into typical imaging features of rare tumors, especially in view of the increasing molecular-driven subtyping.

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Introduction

Increased knowledge about the molecular biology and clinical behavior of rare CNS embryonal tumors have led to substantial advancements and revisions in their classification. The World Health Organization (WHO) classification of CNS tumors previously included the morphologically defined diagnosis of primitive neuroectodermal tumors of the CNS (CNS-PNET) , which represented a heterogeneous group of highly malignant CNS tumors mainly occurring in children, adolescents, or young adults[1]. Identification of an increasing number of molecular markers and genetic alterations has substantially advanced diagnostic specificity and prognostic precision as groundwork for improvement of treatment strategies. The update of the WHO classification in 2016 included the fundamental change of integrating genotypic features into previously mostly histologically defined tumor entities[2,3]. This also fit with observations that embryonal tumors, once generally thought to be associated with a dismal prognosis, actually have a highly variable outcome[4]. The term CNS-PNET was removed from the 2016 update of the WHO classification as it also became apparent that CNS-PNET had included many already known entities such as embryonal tumors with multi-layered rosettes (ETMR) or atypical teratoid-rhabdoid tumors (ATRT) amongst others[5]. In addition, DNA methylation analyses revealed several new tumor types within this group, one of which is the 'CNS neuroblastoma, *FOXR2*-activated' (CNS NB-*FOXR2*) that in the most recent edition of the WHO classification of CNS tumors has been included in the embryonal tumor group[2].

Available clinical data so far suggest that favorable rates of overall survival can be achieved for patients with CNS NB-*FOXR2*, when treated with surgical resection, craniospinal irradiation, and chemotherapy[4,6]. Imaging characteristics suggesting the diagnosis are

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currently based on the description of single patients[7,8], and to the best of our knowledge, larger case series are not available yet. The reason is undoubtedly the increasingly detailed tumor classification, which results in low incidences of confirmed cases in single centers, making international collaboration to pool cases essential.

The aim of this paper was to describe the imaging characteristics of CNS NB-*FOXR2* tumors within an international patient cohort.

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Materials & Methods

The cohort is based on the previously published cohort of pathology samples with original diagnosis of CNS-PNET and molecularly reclassified as CNS NB-*FOXR2*.[4] This study was evaluated and approved by the ethics board of the coordinating institution. Participating international centers had respective IRB clearances to enable them to pool data together. Molecular diagnosis was confirmed by DNA methylation classification (version 11b4 or higher; www.molecularneuropathology.org)[9] in each included case. Imaging data for two of the cases have been published previously.[7]

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The image evaluation team consisted of at least one local neuroradiologist. In joint online meetings on a weekly basis over a period of 12 weeks, consensus decisions were made regarding the following characteristics on pseudonymized images: (1) location, (2) cortical and/or white matter involvement, (3) assumed tumor origin, (4) calvarial involvement, (5) volume (calculated [transverse × craniocaudal × antero-posterior diameter]/2) , (6) strength of enhancement compared to the choroid plexus (none, mild, intermediate, strong), (7) extent of enhancement (in categories: 0 %, 0-25%, 25-50 %, 50-75 %, 75-100 %, or 100 % of

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the solid tumor component), (8) T2WI intensity compared to unaffected cortex, (9) susceptibility indicating calcification and/or hemorrhage on gradient echo imaging (T2* or SWI, potentially further specified by CT, T1WI, T2WI), (10) average ADC_{min}, ADC_{mean}, ADC_{max} values (± standard deviation, SD) in a region of interest (ROI, 0.14-0.65 cm^2 of size) in visually determined areas with lowest values, (11) multifocality, (12) multilobulated appearance, (13) the presence/extent of perifocal edema (in categories: no, < 25% of the perimeter, 25-75%, 100%) (14) the presence of non-solid components (thin-walled cysts and/or necrotic regions with irregular and thick borders), (15) extent of non-solid components (in categories: 0 %, 0-25%, 25-50 %, 50-75 %, 75-100 %, or 100 % of solid to entire tumor), (16) presence and extent of hydrocephalus (in categories: none, mild with ventricular dilation, moderate with ventricular dilation and periventricular edema, severe with additional sulcal effacement)[10], (17) laminar and/or nodular intracranial and/or spinal metastases. Results of arterial spin labeling (ASL) perfusion-weighted imaging or single-voxel MR spectroscopy (SVS MRS) if available. Descriptive statistics were summarized using median / interquartile range (IQR) for non-normally distributed data and mean / ± standard deviation (SD) for normally distributed nominal data. All other variables were reported as percentages.

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Results

Patients

MRI data of 25 treatment-naïve patients with CNS NB-*FOXR2* were included in the analysis. The respective patients (13 females) were diagnosed between 2003 and 2021. The median age was 4.5 years (IQR, 3.1-9 years, ranging from 1.4 to 16 years).

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Imaging

MRI data consisted of T1WI, T2WI, FLAIR as well as contrast-enhanced T1WI for all patients, gradient-echo imaging (T2* or SWI) for 14 patients, and DWI for 21 patients. Arterial spin labeling (ASL) PWI and single-voxel MRS (short TE) were performed in one patient. All MRI scans were acquired before total/partial/subtotal tumor resection. In one patient, MRI was done after the insertion of an external ventricular drain, all other patients were treatment naïve. Four patients also had a baseline CT scan.

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Imaging features

Representative imaging features in different patients are shown in Fig. 1 and further examples of these and other patients are included as online figures. The most frequently affected brain region was the frontal lobe (72%), followed by the parietal (44%) and temporal lobes (36%) as well as the basal ganglia (32%); Typically, more than one region was involved. In most cases (80%), one or two anatomical compartments were involved, mostly the frontal lobes with or without the basal ganglia/thalami. In the majority of cases, the tumor was near the ventricular system without normal tissue visible between the tumor edge and the ventricular wall. Often, the ventricular wall was infiltrated (64%; example in Fig. 1A). In 60% of cases, the right hemisphere was affected. The white matter was always infiltrated. In 20% of cases, the overlying cortex was compressed, but not infiltrated, whereas in the remaining cases, the cortex was also involved. We found it overall difficult to determine where the tumors might have originated owing to their large sizes, but assuming that the epicenter of the tumor usually reflects the origin, 52% appeared to originate in the white matter, followed by the cortex (32%). In only 8% of cases, the tumors seemed to originate from the deep grey matter and/or the white matter of the internal capsule. They never occurred in the brainstem or the infratentorial compartment. The average tumor size was 115 ± 83 ml and was often larger in the 48% of cases with associated skull remodeling

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and scalloping (148 ± 68 ml vs. 85 ± 87 ml; an example of skull remodeling is given in Fig. 1G). Calvarial remodeling was found in 48%, associated with calvarial signal changes in 33%. Most tumors showed intermediate, but inhomogeneous enhancement of the solid components, around necrotic elements (Fig. E-F), or often within the cyst walls. Dural infiltration was noted in two cases. In all cases, the solid component was at least in some parts T2WI hyperintense compared to normal cortex, but increasingly heterogeneous in larger tumors with T2WI hyper-, iso-, and hypointensity (Fig. 1A-B). The signal loss was noted in 43% of cases with available SWI or T2* data (Fig. 1C). It was not possible to confidently determine the cause of increased susceptibility (hemorrhage vs. calcification) even if phase images were available. However, in three patients, calcifications were unequivocally identified by CT and in one patient, associated fluid levels confirmed the presence of hemorrhage on MRI. Altogether in 48% cases, calcifications and/or hemorrhages were diagnosed based on a combination of T1w, T2w, T2*, SWI, and the B0 series of DWI data. ADC values varied considerably between and within tumors (Fig. 1D), but generally low values were probed in the solid portion with an average ADC_{mean} 687.8 ± 136.3×$10^{-6}$$mm^2$/s. Most tumors showed a multilobulated appearance (64%; Fig. 1A-F) and 20% were multifocal. Perifocal edema was not particularly pronounced and at most of intermediate degree. Almost all tumors had non-solid parts (Fig. 1A-B and E-F) except the second smallest, which had a volume of only 10.5 ml. Unequivocal necrosis with thick, irregular, enhancing walls was diagnosed in 16% of cases (Fig. 1A and E), cysts in 25%, and both in another 25%. Metastases were detected in five cases (20%), all of them of nodular appearance and in the CSF spaces. One patient (4.5-year-old boy) had both spinal and ventricular dissemination, the others only cranial. Results are summarized in Table 1.

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A high lipid and lactate peak was noted in the enhancing part of the one case with available MRS. The NAA/Cr ratio was decreased (0.8 in the enhancing, 0.96 in the non-enhancing part), the Cho/NAA and Cho/Cr increased (Cho/NAA 3.12 and 1.74 for the enhancing and non-enhancing part; Cho/Cr 2.5 and 1.66, respectively) altogether compatible with a malignant profile. CBF was elevated on ASL data in the same patient.

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The tumor of one patient, a 5-year-old boy presenting with seizures, was initially suspected to represent a focal cortical dysplasia based on MRI findings (Fig. 2A). He was treated for epilepsy under regular MRI surveillance. After eight months, a growing lesion was observed (Fig. 2B) and after total resection, a CNS NB-*FOXR2* tumor was confirmed.

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Discussion

CNS NB-*FOXR2* has recently been added as tumor type in the 2021 WHO classification of CNS tumors. Therefore, only a few case series describing its imaging features exist [7,8,11–14]. In our international cohort of 25 patients, we found that these were supratentorial, often large, multilobulated tumors with little or no perifocal edema. Tumors nearly always showed a mix of solid and cystic/necrotic components. Involvement of the cortex was present in the majority of cases and the white matter was involved in all patients. Lesions showed intermediate and inhomogeneous contrast enhancement and high vascularity with presence of hemorrhage. Interestingly, a large number of tumors presented with calcifications. The epicenter of the tumor, i.e. the assumed origin, appeared to be in the periventricular and subcortical white matter or the cortex. In almost half of the cases, the adjacent skull was remodeled with thinning of the inner table, and in some cases, pathological signal changes in the affected bone were present. The T2WI intensity in the

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solid parts was heterogeneous, but always hyperintense to grey matter. The ADC values were relatively low, but fluctuated considerably within the solid components. Multifocality and dissemination were seen, but rare.

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CNS NB-*FOXR2* tumors in our cohort showed several imaging features suggesting a high-grade malignancy, such as low ADC values, large volumes, and necrosis. However, they also showed characteristics of less aggressive tumors including T2WI hyperintensity, little perifocal edema and remodeling of the skull. The imaging characteristics described in our study are not specific and especially other embryonal tumors such as ETMR, 'CNS tumor with *BCOR* internal tandem duplication' (CNS *BCOR*-ITD), ATRT, or ependymoma need to be considered in the differential diagnosis. Of these tumors, CNS NB-*FOXR2* are the only type that, to the best of our knowledge, have exclusively presented in a supratentorial location, whereas the other tumor types can develop infratentorially with varying frequencies[4,11,12,14–20]. In addition, patient age may help with differentiation as median age at diagnosis for patients with CNS NB-*FOXR2* is five years (range, 1-20 years), while patients rarely present within the first two years of life.[4] In contrast, ATRT patients are typically younger than 2 years of age with 33% younger than one year at diagnosis.[21] ETMR usually present within the first four years of life[4,22,23], and the median age for presentation with CNS *BCOR*-ITD lies at four years (range, 0.6 to 22 years). The presentation age for supratentorial ependymomas is highly dependent on the molecular subtype. Supratentorial ependymoma, *YAP-1* fusion positive, occur at a median age of 1.4 years,[24] while *ZFTA* fusion-positive ependymoma present at a median age of eight years (largely overlapping with tumors previously diagnosed as ependymoma, RELA fused).[24,25]

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The discrepancy between restricted diffusion, usually attributed to high cellularity, and high signal on T2WI that is typically seen in low proliferative processes has previously been described in ATRT.[15] High cellularity is, however, only one of multiple causes for restricted diffusion. The composition of the tumor matrix (e.g., microcalcifications and hemorrhages, vessels, intracellular structures, or tissue compression) can all contribute to low ADC values without necessarily decreasing the T2w signal.[26] With the current data, we are not able to specify this in more detail. Skull remodeling was found in nearly half of our cases. While this is a relatively common feature in low-grade CNS tumors, we found additional calvarial signal changes in some of these cases, which has also been described in ATRT.[20]

Only one previously published case can be compared to our series,[8] because the two patients described previously by Holsten et al. are included in our cohort.[7] However, since the focus of the case report by Furuta et al. was not primarily on imaging characteristics, the comparison remains limited.[8] Furuta et al. also found a relatively large, partially enhancing, centrally necrotic tumor with scattered calcifications, but in their case with extensive perilesional edema.

As stated previously, some of the cases we included represent a sub cohort of a previously published pathology series of retrospectively re-classified CNS NB-*FOXR2* tumors[4]. In this study, of 307 tumors with an initial diagnosis of CNS-PNET, 36 (12%) were classified as CNS NB-*FOXR2* by DNA methylation profiling in this series. In a pooled cohort of 63 CNS NB-*FOXR2* patients, that includes additionally identified cases, the 5-year progression-free survival and overall survival was 63 and 85%.[4] Frequency of relapses were lowest amongst patients treated with surgical resection, craniospinal irradiation combined with

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chemotherapy. This finding is in agreement with another published series, that includes overlapping patients.[6]

We did not use the *Visually AcceSAble Rembrandt Images* (VASARI) criteria [27] for our assessments as the criteria was not judged fit for our purpose, too detailed in some respects, and not pediatric specific.

Due to the retrospective nature of our study, the imaging data was sometimes incomplete (e.g., missing DWI and T2*/SWI series). While CT images were especially helpful in verifying calcifications or bony changes, they were only available for four patients. In addition, advanced MRI may have been useful to characterize the tumors in more detail, e.g. by shedding some light on neo-angiogenesis with PWI or on metabolic and microstructural changes by MRS or advanced diffusion-weighted techniques, but the multi-institutional approach and the long inclusion period of more than 18 years due to the rarity of these tumors precluded availability of these imaging techniques within this study.

The integrated diagnosis of molecular and morphologic features in CNS tumor diagnostics has radically changed the classification system. The knowledge of an increasing number of molecular profiles and the revision of previous classification groups has and will entail a far more detailed taxonomy. Multicenter collaboration becomes pivotal, as cases become rarer and tumor entities will have to be deep phenotyped through consensus reading. Our experience with weekly joint online meetings was excellent to achieve this objective.

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In conclusion, we describe typical imaging characteristics of CNS NB-*FOXR2* tumors in a multi-center series of 25 patients, the largest to date. Our findings contribute further to the description of new tumor types included in the 5th edition of the WHO classification of CNS tumors.

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Acknowledgement

We thank Magnus Sabel and Elizabeth Schepke (Queen Silvias Children´s Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden) Stefan Rutkowski (Dept. of Paediatric Haematology and Oncology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany), Barbara von Zezschwitz (Dept. of Pediatric Oncology and Hematology, Charité - Universitätsmedizin Berlin, Germany), Darren Hargrave (Pediatric Oncology Unit, UCL Great Ormond Street Institute of Child Health, London, UK), Tom Jacques (Developmental Biology and Cancer Research & Teaching Department, UCL Great Ormond Street Institute of Child Health, London, UK) and Pieter Wesseling (Department of Pathology, Amsterdam University Medical Centers/VUmc, Amsterdam, the Netherlands) for contributing clinical and molecular data.

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27. Visually AcceSAble Rembrandt Images (VASARI). Accessed May 29, 2022. https://wiki.cancerimagingarchive.net/display/Public/VASARI+Research+Project

Table:

anatomical localization (% of cases)*	frontal 72% parietal 44% temporal 36% basal ganglia 32% sellar/suprasellar 20% occipital 12% thalamic 8% brainstem 4% cerebellar 4% spine 4%
number of involved anatomical compartments (% of cases)	one 36% (32% frontal, 4% parietal) two 44% (16% frontal/deep GM, 4% temporal/deep GM, 8% fronto-parietal, 8% fronto-temporal, 4% parieto-occipital, 4% temporo-parietal) three 8% (4% temporo-parieto-occipital, 4% fronto-tempral/deep GM) four 12% (8% fronto-temporo-parietal/deep GM, 4% fronto-temporo-

	parieto-occipital)
regional involvement (% of cases)*	cortex 80% white matter 100%
assumed tumor origin (% of cases)*	white matter 52% cortex 36% deep grey matter 8% equivocal 8%
calvarial co-response (% of cases)	calvarial remodelling 48% signal changes in the remodeled bone 16% (33% of the remodeled bone)
volume (mean; SD)	115 ± 83 ml
strength of enhancement (compared to choroid plexus; % of cases)	no 8% mild 20% intermediate 60% strong 12%
enhancement (% of entire tumor; % of cases)	no 8% 0-25% in 8% 25-50% in 16% 50-75% in 4% 75-100% in 60% 100% in 4%
T2w intensity (compared to cortex; % of cases)*	hyperintense 100% isointense 48%

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	hypointense 44%
calcification/hemorrhage (% of cases)	calcification only in 12% hemorrhage only in 16% calcification and/or hemorrhage in 20%
ADC (mean ± SD in $10^{-6}mm^2/s$)	ADC_{min} 547.2 ± 114.2 ADC_{mean} 687.8 ± 136.3 ADC_{max} 830.2 ± 207.8
multifocality (% of cases)	20%
multilobulated appearance (% of cases)	64%
perifocal edema (% of cases)	no 24% little 60% intermediate 16% extensive 0%
tumors with non-solid parts (cystic/necrotic parts; % of cases)	entirely solid 4% 0-25% in 24% 25-50% in 32% 50-75% in 16% 75-100% in 24%
hydrocephalus	no 32% mild 24% moderate 32% severe 12%
metastases in the CSF spaces	20% (all cerebral, one cases cerebral &

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	spinal), all nodular

Tab. 1: Imaging features. Consensus decisions are reported in percentage of cases and as mean ± standard deviation (SD) values for ADC and tumor volume. *Percentages can exceed 100%, because tumors can be located in several regions or be of heterogeneous signal intensity. GM: grey matter.

Figure captions:

Fig. 1: Typical imaging characteristics of CNS NB-*FOXR2* in different patients (A: 2.5-year-old girl; B, F, G: 3-year-old girl; C: 4.2-year-old girl; D: 4-year-old boy; E: 2.7-year-old boy). Most tumors were characterized by T2WI signal heterogeneity, but mostly hyperintense compared to cortical grey matter (A, B). In the majority, no or little perifocal edema (arrow in A) was found. When gradient-echo images (T2*, SWI) were available, signal loss was detected in about half of the cases (C). In general, ADC values were relatively low. An example is given in D: ADC_{mean} in a region-of-interest (ROI) placed within the solid tumor component is 660 $*10^{-6}mm^2/s$ (ADC_{min} $550*10^{-6}mm^2/s$, ADC_{max} $760*10^{-6}mm^2/s$). Contrast enhancement on T1WI was mostly mild to intermediate compared to the choroid plexus and seen in larger parts of the solid component (E). Non-solid tumor components with thick, irregular borders were often noted representing necrotic regions (E). The main tumor load was often located in the white matter with compression (arrowhead in A) or infiltration (star in E) of the overlying cortex or it appeared to originate from the cortex (B). Skull remodeling was detected in about half of the cases (arrow on CT in F), often associated with bony signal changes (arrowhead, G).

Fig. 2: Axial FLAIR of a 4.5-year-old boy presenting with seizures. Initially called a focal cortical dysplasia of the right frontal lobe (A). The follow-up MRI 8 months later showed

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disease progression (arrow in B). After resection, the diagnosis of a CNS NB-*FOXR2* was made.

Online figure (one patient per row; the patient ID refers to evaluation_results.xlsx):

A: A 3-year-old girl (patient ID 004) with a large (155.6 ml) CNS NB-*FOXR2* in the right frontal lobe extending into the basal ganglia, thalamus, suprasellar region and infiltrating the wall of the right lateral ventricle and the third ventricle. The cortical ribbon is not involved, only affected by subtle perifocal edema (yellow arrow), and the tumor origin was assumed in the white matter. Large necroses with thick, irregular, contrast-enhancing borders are noted (blue arrows). The lesion is hyperintense on DWI (ADC not available).

B: A 4-year-old boy (patient ID 017) with a tumor (217.0 ml) in the left frontal lobe and basal ganglia close to, possibly infiltrating the left ventricle. The cortex is infiltrated (yellow arrows). ADC values were low (ADC_{min} 550.0*$10^{-6}$$mm^2$/s, ADC_{max} 760.0*$10^{-6}$$mm^2$/s, ADC_{mean} 660.0 *$10^{-6}$$mm^2$/s). The tumor is partially necrotic (blue arrows) and shows intermediate, inhomogeneous enhancement. Hydrocephalus is moderate.

C: A 2.1-year-old girl (patient ID 008) with a multilobulated, inhomogeneously enhancing, T2WI hyperintense tumor (11.9 ml) in the right frontal and temporal lobe with a small suprasellar component. Multifocality with nodules in the inferior frontal gyrus, the frontobasal cortex, and the deep grey matter is shown (yellow arrows). The right olfactory bulb is jnfiltrated as well (blue arrow).

D: A 2.7-year-old boy (patient ID 010) with a left frontal tumor (157.1 ml) infiltrating the lateral ventricle. There is weak and inhomogeneous enhancement (yellow arrow) and small hemorrhagic foci (blue arrows).

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E: A 4.1-year-old girl (patient ID 029) with a hemorrhagic tumor (141.8 ml) involving the left frontal lobe, the basal ganglia, and the thalamus extending to the midline and the sellar/suprasellar region. There is extensive hydrocephalus and the ventricular wall is likely to be infiltrated. Although large parts of the cortex are infiltrated (yellow arrows), the tumor has presumably originated in the frontal white matter. Susceptibility is noted on SWI, partly corresponding to T1WI hyperintensity (blue arrows), likely to represent both calcification and hemorrhage. CT was not available and a definite decision could not be made.

F: A 10-year-old girl (patient ID 019) with a partially cystic tumor (125.0 ml) in the right parietal lobe. Opposed to necrosis (shown in A and H), cysts were defined as thin-walled non-solid components. In this case, the cyst contents are slightly T1WI hyperintense and a small posterior fluid level (blue arrow) is noted, indicating intracystic hemorrhage. The T2WI intensity of the solid component is relatively low, but still slightly higher than that of the normal cortex. The lowest ADC values were ADC_{min} 428.0*$10^{-6}$$mm^2$/s, ADC_{max} 713.0*$10^{-6}$$mm^2$/s, ADC_{mean} 536.0 *$10^{-6}$$mm^2$/s.

G: A 4.5-year-old boy (patient ID 023) with a left-sided temporo-parietal tumor (170 ml) infiltrating the ventricular system. Note the small, nodular metastases in the frontal horn of the lateral ventricles (blue arrows). The tumor is very vascular with large intralesional vessels (yellow arrows) and CT demonstrates coarse calcifications. There is moderate to extensive hydrocephalus.

H: A 2.5-year-old girl (patient ID 025) with the largest tumor in our cohort (340.5 ml). It is located in the left frontal and parietal lobes, multilobulated, shows intermediate and relatively homogeneous enhancement and extensive susceptibility on SWI that represented calcifications (verified on CT, not shown here). Several necrotic regions are noted (some of them pointed out by blue arrows).

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