CNS embryonal tumours: WHO 2016 and beyond

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Keywords: embryonal tumour – medulloblastoma – embryonal tumour with multilayered rosettes – atypical teratoid/rhabdoid tumour – World Health Organisation

Words: 2584 (main body of text), figures: 1, tables: 2

Abbreviations: AT/RT atypical teratoid/rhabdoid tumour; CNS central nervous system; ETANTR embryonal tumour with abundant neuropil and true rosettes; ETMR embryonal tumour with multi-layered rosettes; FISH fluorescence *in situ* hybridisation; IHC immunohistochemistry; MB medulloblastoma; NOS not otherwise specified; PNET primitive neuro-ectodermal tumour; WHO World Health Organisation.

For publication in Neuropathology and Applied Neurobiology.

Abstract

Embryonal tumours of the CNS present a significant clinical challenge. Many of these neoplasms affect young children, have a very high mortality and therapeutic strategies are often aggressive with poor long-term outcomes. There is a great need to accurately diagnose embryonal tumours, predict their outcome and adapt therapy to the individual patient's risk. For the first time in 2016, the WHO classification took into account molecular characteristics for the diagnosis of CNS tumours. This integration of histological features with genetic information has significantly changed the diagnostic work-up and reporting of tumours of the CNS. However, this remains challenging in embryonal tumours due to their previously unaccounted tumour heterogeneity. We describe the recent revisions made to the 4th edition of the WHO classification of CNS tumours and review the main changes, whilst highlighting some of the more common diagnostic testing strategies.

Introduction

Since the last version of the WHO classification of tumours of the CNS in 2007 (1), molecular investigation has revolutionised our understanding of embryonal tumours of the CNS. This has largely been driven by genome-wide studies characterising prevalent genetic events and biological features. These have led to tumour reclassification, sub-typing and identification of novel entities (2,3). However, many unanswered questions remain about the clinical impact of this knowledge, the best way to implement testing in clinical practice and how to manage the tumours that, despite molecular advances, defy standard classification.

Implementation of the integrated diagnosis for embryonal tumours
While the WHO classification 2007 relied on histological features only, the challenge of its update in 2016 was to integrate meaningful genetic information to enable a more precise classification, while maintaining continuity with the previous editions (4). This integrated diagnosis would be presented in a layered format; including the histological diagnosis, WHO grade, molecular genetic information and ultimately the integrated diagnosis. The value of this approach is clearly illustrated in embryonal tumours, in particular medulloblastoma, where the combination of molecular and histological data provides discrete diagnostic information (Figure 1) (2,4).

For non-medulloblastoma and non-AT/RT embryonal tumours, diagnostic classification has been a major challenge. These tumours were formerly called supratentorial or CNS-primitive neuro-ectodermal tumours (PNET) (1). Up until now, "CNS-PNET" has been used as an umbrella term for a range of biologically different tumours. Several molecular profiling studies

on tumours previously diagnosed as CNS-PNET showed that a wide range of biologically different tumours existed within this entity, some of which were incorrectly assigned (5-7). These encompassed other well-recognised tumour types (e.g. high-grade gliomas and sarcomas), recently redefined entities (e.g. embryonal tumour with multi-layered rosettes, ETMR) as well as novel tumour types (2).

The clinical importance of molecular classification

The correct diagnosis of paediatric tumours is critical for their treatment because of the balance required between achieving a long-term cure and avoiding treatment related disability in survivors. It is essential to recognise those children with a poor prognosis who can either receive escalated treatment or be offered palliative care, versus those with a good prognosis for whom treatment might be reduced to prevent long term complications. This is perhaps again best illustrated in medulloblastoma, where overall survival rates are 65-70% after 5 years (8). However, there are significant cognitive, endocrine and neurological complications in the majority of survivors (9,10). These individuals are significantly less likely to complete education and live independently when compared to age matched controls.

Medulloblastoma

Four medulloblastoma genetic entities are now recognised by WHO 2016 classification (4). These are: 1) WNT-activated (MB_{WNT}); 2) SHH-activated (MB_{SHH}), *TP53* wildtype; 3) SHH-activated (MB_{SHH}), *TP53* mutant; 4) Non-WNT/Non-SHH medulloblastoma. The latter can be further subdivided with DNA methylation or mRNA expression profiling into "group 3" and "group 4" (11). These variants are considered provisional because it is not absolutely clear to what extent they represent distinct diseases, multiple subtypes or variants of a single entity. Table 1 describes their most commonly associated genetic changes and the diagnostic histological variants. It is essential that according to the revised WHO classification 2016, every diagnosis of medulloblastoma should result in an integrated diagnosis with a histological part and a genetically defined part as both aspects provide clinically important information (12).

Genetically defined medulloblastoma

Around 10% of medulloblastomas fall into the MB_{WNT} subgroup and most display classic histology (3). Over 90% of MB_{WNT} are associated with point mutations in exon 3 of the *CTNNB1* (beta-catenin) gene. Mutations in *CTNNB1* or (at lower frequencies) other components of the WNT signalling pathway (e.g. *AXIN1, AXIN2* and *APC*) lead to the pathway's constitutive activation with accumulation of the ß-catenin protein in the nucleus, identifiable by immunohistochemistry (IHC). Monosomy for chromosome 6 is present in about

85% of cases, and may aid in supporting a diagnosis of MB_{WNT}. Importantly, MB_{WNT} has an excellent overall prognosis in children (>90% survival) following surgery and current treatment protocols (3). Clinical trials are underway in Europe and North America to determine if treatment intensity can be safely reduced for these tumours, thus also reducing treatment-related long term developmental and cognitive disabilities without affecting survival rates (13). However, it should be noted that the adults with MB_{WNT} do not show the same prognostic advantage (14).

Approximately 30% of medulloblastomas show activation of the sonic hedgehog signalling pathway signalling (3). The status of *TP53* further divides MB_{SHH} into two entities with completely different clinical outcomes (15). MB_{SHH} tumours with *TP53* mutations have a dismal prognosis and are considered very high-risk. A significant number of these patients (~50% in one series) carry germline mutations in *TP53* and their treatment is especially challenging due to their susceptibility to secondary tumours following radiotherapy (16). MB_{SHH} patients without *TP53* mutations are considered lower-risk but many of these, particularly young children, carry germline mutations in *PTCH1* or *SUFU* which can alter treatment strategies (17). Therefore, genetic counselling should be considered for all families with children with medulloblastomas with SHH activation.

Non-WNT/non-SHH medulloblastomas are provisionally divided into group 3 (MB_{grp3}) and group 4 (MB_{grp4}), which account for approximately 20% and 40% of all medulloblastomas respectively. However, the diagnostic status of the non-WNT/non-SHH subtypes is likely to develop over the next few years.

Histologically defined medulloblastoma
The histological subtypes of medulloblastoma have not changed in a major way in the update of the 4th edition of the WHO classification (see Table 1) (1,4). Large cell and anaplastic variants have been combined into a single entity, reflecting their frequent coexistence together with the clinically uniform approach to this group. This tumour type has a very poor prognosis. Furthermore, the melanotic and myoblastic forms have been regarded as tissue patterns rather than specific entities, reflecting their extreme rarity. Finally, an emphasis is made in defining the desmoplastic/nodular medulloblastoma subtype by reticulin staining. The key feature in defining this subtype is that the nodules are surrounded by reticulin-rich tissue. This allows distinction between classic medulloblastoma with a biphasic architecture, which has nodules but no desmoplasia (regarded as a variant of classic medulloblastoma) from desmoplastic/nodular medulloblastoma which has not only nodular architecture but extensive reticulin rich desmoplasia between the nodules.

Overlap exists between molecular and histological subtypes; for example, MB_{WNT} almost always has classic histology, while desmoplastic/nodular MB and MB with extensive nodularity are MB_{SHH}. However, MB_{SHH} can have classic or anaplastic histology and occasional anaplastic MB_{WNT} cases have been reported. The interplay between molecular and histological subtype is imperfectly understood and their relationship to outcome is yet to be addressed in a systematic way.

Prognostic markers of medulloblastoma

In addition to the molecular techniques needed to classify medulloblastoma, there are molecular markers that provide additional prognostic information. The two markers for which there is the best data and are offered routinely are amplification of *MYC* or *MYCN*; presence of either of these has been associated with a worse outcome (18). However, recent data suggests that the prognostic significance of these markers depends on the genetically defined medulloblastoma entity. *MYC* amplification is usually seen in non-WNT/non-SHH medulloblastomas and these patients have a poor prognosis. While amplification of *MYCN* in MB_{SHH} indicates a very poor outcome, its prognostic value in non-WNT/non-SHH medulloblastomas is less clear (8).

Recent classification of medulloblastoma

Larger datasets have recently suggested more medulloblastoma subgroups than the current WHO recognises. One study proposes seven genetic entities based on clustering algorithms, with each existing group except MB_{WNT} being further divided into high and low-risk (8); while another suggests a total of 12 subgroups based on the integration of transcriptomic and methylation data (19). Further exploration of the clinical significance of these subtypes will reveal how the next WHO classification may need to be adapted.

Relapsed medulloblastoma

Relapsed medulloblastoma has a uniformly bad outcome (20). There is a great need to understand the tumours at the point of relapse, especially their mechanisms of resistance. At relapse, medulloblastoma has been shown to maintain the same genetically-defined subtype but may change morphological subtype, for example towards a more anaplastic pathology (21). Furthermore, acquisition of additional genetic events at relapse can also have a clinical impact. Combined abnormalities of *MYC* and *TP53* occur in a subpopulation of relapsed medulloblastoma and are associated with a very poor prognosis (22). In mouse models, these tumours can be targeted therapeutically and suggests that it will be important

to undertake diagnostic testing on the relapsed tumour both to predict outcome but also to predict response to treatment.

Spatial heterogeneity studies in medulloblastoma suggest that actionable drug targets (i.e. mutations) are unevenly distributed across the tumour mass (23). This indicates that subclonal events underlying tumour heterogeneity may be responsible for drug resistance, which also puts into question the efficacy of targeted monotherapies, especially in the presence of subclonal events at relapse (24).

Non-medulloblastoma embryonal tumours

Embryonal tumour with multilayered rosettes (ETMR)
The recognition of embryonal tumour with multilayered rosettes, *C19MC*-altered as a distinct tumour type is a major change in recent years. Historically, these tumours have been described under a range of morphological entities: embryonal tumour with abundant neuropil and true rosettes (ETANTR), ependymoblastoma and medulloepithelioma (Figure 1) (25). These tumours harbour an amplification on chromosome 19 of a large miRNA cluster (*C19MC*) (26,27), which can be readily identified by FISH. This region is associated with a suspected area of genetic instability, leading to the fusion of *TTYH1* with *C19MC* (28). Although not specific to ETMRs, LIN28A is typically expressed in ETMRs (LIN28A is also expressed in some germinomas and occasionally in AT/RT) and detection by IHC is a useful screening test to alert to the possibility of an ETMR and the need for *C19MC* amplification testing (29). The clinical behaviour of ETMR is typically that of rapid progression and in most cases, they are unresponsive to conventional therapy. Therefore, immunohistochemically, molecularly and clinically, ETMRs form a relatively uniform group of infant CNS tumours with generally abysmal outcomes. Many of the tumours previously called medulloepithelioma will fall into this group but there are medulloepitheliomas that while expressing LIN28A, lack *C19MC* amplification (6) which according to the current WHO classification should be regarded as a separate entity (4). Finally, ETMR, NOS should be assigned when multilayered ependymoblastic rosettes are identified, but there is no *C19MC* alteration detected or when testing for the alteration has not been undertaken.

Atypical teratoid/rhabdoid tumours (AT/RT)
AT/RT has been a well-established tumour entity for many years and has been recognised in previous editions of the WHO (1). However, the demonstration of *SMARCB1* (*INI1*) loss or very rarely loss of *SMARCA4* (*BRG1*), also a component of the SWI/SNF chromatin remodelling complex, has become a diagnostic requirement (Table 2). This reflects the long-

accepted definition of these as high-grade CNS tumours characterised by inactivation of these genes (30). In instances where tumour morphology is consistent with AT/RT but displays positive nuclear staining for *SMARCB1, SMARCA4* loss should be confirmed.

Several studies have indicated the presence of molecular AT/RT subtypes associated with differences in clinical and treatment responses and consensus is underway in order to better inform molecular stratification of these tumours and determine if this will become clinically relevant (31,32). A separate category for CNS embryonal tumour with rhabdoid features has been retained for tumours in which either the genes are intact or their status cannot be determined (4).

Other CNS embryonal tumours
The generic term 'embryonal tumours' has replaced CNS primitive neuroectodermal tumours (CNS-PNET) in the WHO 2016 classification (Figure 1). This separates the current terminology from historical concepts of PNET covering a diverse range of CNS tumours (medulloblastoma and supratentorial PNET) and from potential confusion from tumours of the same name arising outside the nervous system (e.g. Ewing's type sarcoma/peripheral PNET) (33,34). CNS embryonal tumours include the following morphological subtypes: medulloepithelioma, CNS neuroblastoma, CNS ganglioneuroblastoma and CNS embryonal tumour, NOS. The diagnosis of embryonal tumour therefore requires active exclusion of other embryonic specific entities (e.g. ETMR and AT/RT). Furthermore, a proportion of tumours previously described as CNS-PNET can be re-diagnosed as a number of other tumour types (e.g. glioblastoma, ependymoma, Ewing's sarcoma) (35,36) and these must also be excluded. Table 2 includes an overview of useful diagnostic IHC testing that can be performed with respect to making a diagnosis of embryonal tumour.

Recent data has defined four tumour entities based on methylation profiling; some of which historically would have been diagnosed as CNS-PNET, along with other tumour types (36). Sequencing for recurrent mutations identified common gene fusions in a proportion of cases belonging to these subgroups. CNS neuroblastoma with FOXR2 activation (NB-FOXR2) was characterised by *FOXR2* fusions, which may come to encompass CNS neuroblastomas and CNS ganglioneuroblastomas. High-grade neuroepithelial tumours with MN1 alteration (HGNET-MN1) typically contain *MN1* fusions (identifiable by FISH), although a robust immunohistochemical marker is missing. Morphological similarities have been noted to the glial neoplasm, astroblastoma. The Ewing's sarcoma family tumour with CIC alteration (EFT-CIC) have *CIC* structural variants, which can be detected by break-apart FISH and are typically characterised by positive *NUTM1* nuclear staining. Finally, the BCOR-altered neuroepithelial

tumours are defined by a *BCOR* duplication (and rarely point mutations) in exon 15. Both these entities may reflect mesenchymal/sarcomatous tumours which occur in other parts of the body and not limited to the CNS.

Due to the rarity of these novel tumour entities, risk stratification, assessment of clinical significance and selection of appropriate therapeutic strategies will be immensely challenging. However, preliminary clinical data from a total of 31 patients did suggest differences in survival rates; with the HGNET-MN1 group associated with the best prognosis (36).

Pineoblastoma

Pineoblastomas histologically resemble CNS embryonal tumours but arise from the pineal gland. They are treated according to the same protocols as embryonal tumours and show poor prognosis, although studies suggest that adults and children do better than infant cases (37,38). Histologically, they are composed of sheets of densely packed hyperchromatic cells with strong staining for neuronal markers (e.g. synaptophysin). Cytogenetic studies describe pineoblastomas as having fewer alterations compared with other embryonal tumours (39) and similarly, recurrent genetic changes beyond germline *RB1* mutations (linked to retinoblastoma) and *DICER1* are yet to be identified (40). Retinoblastoma and pineoblastoma can coincide in patients with trilateral retinoblastoma due to common developmental lineages and the retinal transcription factor, CRX has been identified as a possible marker of some pineal tumours, although its interpretation may be somewhat challenging depending on the age and quality of the tissue (41,42).

Pineal anlage tumours are very rare pineal tumours with heterologous differentiation alongside a primitive neuroectodermal component. They typically contain melanin and the heterologous elements may exhibit skeletal muscle or chondroid differentiation (43). There are no molecular studies that indicate whether there are distinctive diagnostic molecular features of this tumour.

Pituitary blastoma

An extremely rare entity that is considered an embryonal tumour of the pituitary gland is the pituitary blastoma (44). There are 13 infant cases described in the literature and a germ-line mutation in *DICER1* is reported to be a key predisposing event (45).

Concluding remarks

In terms of diagnostic approaches, transparency is needed on how molecular and immunohistochemical tests are ideally performed and interpreted for optimal guidance of therapeutic management. For medulloblastoma, recent guidelines for clinical diagnosis have

been published (46) and similar information should be made available for the other entities. DNA methylation and transcriptomic based clustering approaches are proving greatly valuable but are not widely accessible, nor are such methods fully validated for clinical diagnosis. Obviously, insufficient material for genetic screening may lead to uncertainty and not all centres may currently have access to the necessary facilities to implement a fully integrated diagnosis.

Since the publication of the WHO 2016 classification, additional heterogeneity within the medulloblastoma subtypes and other embryonal tumour groups has already been identified (8,19,36) and we anticipate additional molecular findings are likely to influence the next WHO revision. As existing tumour groups are further sub-divided into distinct groups, the rarity of these tumours will challenge risk-stratification and assignment of appropriate therapeutic strategies, while archival studies will be key in identifying defining molecular signatures of currently unclassifiable tumours.

The authors have no conflict of interest to declare

Legends

Figure 1. Summary of the major changes in the WHO 2016 classification for the diagnosis of CNS embryonal tumours

In the 2007 WHO classification tumours were histologically defined. In the current edition, an integrated diagnosis combines histology with genetically defined tumours. For embryonal tumours, this has meant four new genetic subgroups of medulloblastoma. The CNS-PNET entity is no longer recognised, instead ETMRs form their own embryonal entries, while any remaining tumours are currently classified based on histology alone and fall under "other embryonal tumours". This group of genetically undefined tumours contains medulloepithelioma, CNS neuroblastoma, CNS ganglioneuroblastoma and CNS embryonal tumour, NOS. *: provisional subentity, NOS: not otherwise specified.

Table 1. WHO 2016 classification of medulloblastoma subtypes, characterised by genetic and histological features

The most common features associated with each molecular (A) and histological (B) subgroup for medulloblastoma are described. The tables aid as a good basis for completing an integrated diagnosis of medulloblastoma. For a more comprehensive list, the reader is advised to refer to the WHO 2016 classification, pages 184-185.

Table 2. WHO 2016 classification of non-medulloblastoma embryonal tumours

The key diagnostic features associated with non-medulloblastoma embryonal tumours are described. For a diagnosis of embryonal tumours, NOS it is necessary to actively exclude alternative possibilities (e.g. ETMR, high-grade glioma, ependymoma etc.) and if possible, it may be worth considering a DNA methylation array to see if the tumour matches previously identified molecular profiles. For more details, the reader is advised to refer to the WHO 2016 classification, pages 201-212.

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A. Medulloblastoma, genetically defined			
WHO	**Histological**	**Special**	**Key molecular features**
WNT activated	Usually classic	Nuclear β-catenin positive (>5-10% of cells) Nuclear YAP1 positive, nuclear OTX2 positive GAB1 negative, p75NGFR negative	Mutation in exon 3 of *CTNNB1* (β-catenin) Monosomy of chromosome 6 Typical WNT profile on methylation and transcriptome analysis
SHH activated, *TP53* wildtype	Any variant. Includes all nodular/desmoplastic medulloblastomas and MBEN	No significant nuclear β-catenin, Nuclear YAP1 positive, nuclear OTX2 negative, GAB1 positive, p75NGFR positive	No mutation of *TP53* Typical SHH-profile on methylation and transcriptome analysis
SHH activated, *TP53* mutant	Any variant, often anaplastic	No significant nuclear β-catenin, Nuclear YAP1 positive, nuclear OTX2 negative, GAB1 positive, p75NGFR positive, Mostly nuclear p53 positive	Mutation of *TP53* Typical SHH-profile on methylation and transcriptome analysis Frequently *MYCN* or *GLI2* amplification
Non-WNT/non-SHH (Group 3 or Group 4)	Any variant except desmoplastic/nodular or MBEN	No significant nuclear β-catenin Nuclear YAP1 negative, nuclear OTX2 positive GAB1 negative, p75NGFR negative	*MYC* or *MYCN* amplification in some but not diagnostic Typical Group 3 or Group 4 profile on methylation and transcriptome analysis

B. Medulloblastoma, histologically defined			
WHO entity	**Histological features**	**Special stains/ immunohistochemistry**	**Key molecular features**
Classic	Lacks intratumoural desmoplasia or significant (diffuse and severe) anaplasia	Reticulin staining shows a lack of nodular desmoplasia	Frequent phenotype across all 4 molecular categories
Desmoplastic/ Nodular	Nodular with internodular desmoplasia, can be present in minor areas only	Reticulin staining highlights internodular desmoplasia. SHH phenotype (nuclear YAP1 positive, GAB1 positive, p75NGFR positive, nuclear OTX2 negative, no significant nuclear β-catenin)	SHH-activated molecular profiles
Medulloblastoma with extensive nodularity	Abundant and large irregular nodules with internodular desmoplasia	Reticulin staining highlights internodular desmoplasia. Advanced neurocytic differentiation in islands with strong nuclear NeuN expression. SHH phenotype (nuclear YAP1 positive, GAB1 positive, p75NGFR positive, nuclear OTX2 negative, no significant nuclear β-catenin)	SHH-activated molecular profiles

Large cell/anaplastic	Predominant large cell and/or anaplastic phenotype of tumour cells	Large cell cytology is frequently associated with dot-like synaptophysin expression. P53 accumulation may hint to SHH-activated cases with *TP53* mutation.	Mostly non-WNT/non-SHH molecular profiles, also in SHH medulloblastoma, *TP53* mutated. Frequent MYC gene amplification in tumour with large cell phenotype. Anaplasia may hint to *TP53* mutated SHH activated medulloblastomas.

WHO entity	Diagnostic investigations
ETMR, C19MC altered	LIN28A positive [IHC] *C19MC* amplification [FISH or array] or fusion (RT-PCR)
ETMR, NOS	Multilayered ependymoblastic rosettes but *C19MC* alteration either not detected or testing for this alteration not undertaken
Medulloepithelioma	LIN28A positive No detectable *C19MC* amplification
AT/RT	*SMARCB1* or *SMARCA4* loss [IHC sufficient, can be confirmed by sequencing but not required]
CNS embryonal tumour with rhabdoid features	*SMARCB1* and *SMARCA4* retained but showing rhabdoid features
CNS neuroblastoma	Immunohistochemical evidence for neuroblastic/neuronal differentiation (synaptophysin-positive) LIN28A negative, *SMARCB1* and *SMARCA4* retained
CNS ganglioneuroblastoma	Immunohistochemically similar to CNS neuroblastoma but with groups of prominent ganglion cells LIN28A negative, *SMARCB1* and *SMARCA4* retained
CNS embryonal tumour, NOS	Requires active exclusion of other diagnoses: - AT/RT: *SMARCB1* and *SMARCA4* intact - ETMR: no LIN28A expression or *C19MC* amplification - Soft tissue tumours/Ewing's sarcoma: no membranous CD99 [IHC], *EWSR1* or *CIC/NUT* rearrangement not present [FISH, RNA-seq] - Ependymoma: no *C11orf95-RELA* fusion [FISH], L1CAM and/or nuclear p65/RelA expression [IHC] - High grade astrocytoma: no mutations in *H3.1*, *H3.3*, *ATRX*, *IDH1/2* [IHC, sequencing needed to exclude the presence of *H3F3A* G34 mutation] - Consider methylation profiling

WHO 2007

histologically defined

Medulloblastoma
- Classic
- Desmoplastic / Nodular
- Extensive nodularity
- Large cell
- Anaplastic

AT/RT
- Atypical teratoid/rhabdoid tumour

CNS PNET
- Ependymoblastoma
- Medulloepithelioma
- CNS neuroblastoma
- CNS ganglioneuroblastoma

WHO 2016

genetically defined

Medulloblastoma
- WNT activated
- SHH activated-TP53 wildtype
- SHH activated-TP53 mutated
- Non-WNT/non-SHH
- Group 3*   Group 4 *

ET with rhabdoid features
- Atypical teratoid/rhabdoid tumour

ET with multilayered rosettes
- ETMR C19MC-altered

other embryonal tumours

histologically defined

- Classic
- Desmoplastic / Nodular
- Extensive nodularity
- Large cell / Anaplastic

- CNS embryonal tumour with rhabdoid features*
- ETMR, NOS*
- Medulloepithelioma
- CNS neuroblastoma
- CNS ganglioneuroblastoma

Medulloblastoma, NOS

Embryonal tumour, NOS

* provisional subentity
NOS = not otherwise specified
grey lines indicate most prominent associations between histological and genetically defined entities

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