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MINIREVIEWS

Simple approach for the histomolecular diagnosis of central nervous system gliomas based on 2021 World Health Organization Classification

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Abstract

The classification of central nervous system (CNS) glioma went through a sequence of developments, between 2006 and 2021, started with only histological approach then has been aided with a major emphasis on molecular signatures in the 4th and 5th editions of the World Health Organization (WHO). The recent reformation in the 5th edition of the WHO classification has focused more on the molecularly defined entities with better characterized natural histories as well as new tumor types and subtypes in the adult and pediatric populations. These new subclassified entities have been incorporated in the 5th edition after the continuous exploration of new genomic, epigenomic and transcriptomic discovery. Indeed,

the current guidelines of 2021 WHO classification of CNS tumors and European Association of Neuro-Oncology (EANO) exploited the molecular signatures in the diagnostic approach of CNS gliomas. Our current review presents a practical diagnostic approach for diffuse CNS gliomas and circumscribed astrocytomas using histomolecular criteria adopted by the recent WHO classification. We also describe the treatment strategies for these tumors based on EANO guidelines.

Key Words: Central Nervous System glioma; Classification; World Health Organization 2021; European Association of Neuro-Oncology guidelines

Core Tip: Central nervous system (CNS) gliomas went through a sequence of development since 2006. The guidelines of 2021 World Health Organization (WHO) classification of CNS tumors and European Association of Neuro-Oncology (EANO) utilized molecular signatures in the diagnostic approach for CNS gliomas. We herein presents a practical diagnostic approach and the treatment strategies for diffuse CNS gliomas and circumscribed astrocytomas using histomolecular criteria based on the WHO classification.

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INTRODUCTION

Brain tumors are defined as masses derived from various cells originating from the brain (primary tumors) or distally (secondary tumors, most commonly lung, breast, renal, prostate, and skin cancers) that have undergone metastatic spread[1]. The most prevalent primary intracranial tumors are gliomas, with 80% of the population, and World Health Organization (WHO) grade 4 astrocytoma (previously named glioblastoma) is present in nearly one-half of the patients with astrocytoma, with a 95% mortality rate in a 5-year follow-up period irrespective of age and gender[2,3,4]. Gliomas usually present with headache, nausea and vomiting, blurred vision, focal neurological deficit, alteration in sensation, and other manifestations of high intracranial pressure that warrant investigation by neuroimaging, preferably magnetic resonance imaging (MRI) of the brain[5]. In imaging, cystic change, multicentric enhancement, and hemorrhage are commonly observed[6]. Therefore, histopathological examination is considered the gold standard method for diagnosing and grading the tumors.

According to the WHO classification, central nervous system (CNS) gliomas can be classified based on their histological and molecular features[1]. The classification initially includes diffuse and non-diffuse gliomas, and it has undergone significant changes since its establishment to the 4th edition in 2016, aided by molecular signatures[2]. The recent 5th edition of the WHO classification has replaced the entity with type and variant with (subtype) group. In addition, the WHO classification has adopted Arabic numerical over the former Roman numerical grading system for grading brain gliomas for easier reading and to avoid confusion when interpreting pathology reports[7]. However, using the Roman numerical grading system is still considered acceptable. Some of the most important changes in the 5th edition involve the classification of gliomas, differentiating gliomas that occur primarily in adults from those that occur mainly in children[8]. Gliomas are traditionally subclassified into three major categories: diffuse gliomas, pediatric diffuse low- and high-grade gliomas, and circumscribed astrocytic gliomas (Figure 1). In addition, glioneuronal tumors, neuronal tumors, and ependymomas were also included in the classification as separate types[7,8].

Further propositions of the 2021 WHO classification of CNS tumors was adapted by the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy - Not Officially WHO (cIMPACT-NOW), published in 2020/2021. Moreover, they included various molecular genomic studies, including methylation profiling, isocitrate dehydrogenase (*IDH1-2*) codon mutation, and alpha-thalassemia-mental retardation X-chromosome (*ATRX*) mutation. This genomic profiling has affected such tumors' management and treatment modalities[9]. Moreover, three major subtypes of diffuse gliomas have been emphasized, based on molecular genomic signatures, including *IDH*-mutant oligodendroglioma with 1p/19q codeletion, *IDH*-mutant astrocytoma, and *IDH*-wild-type glioblastoma [8].

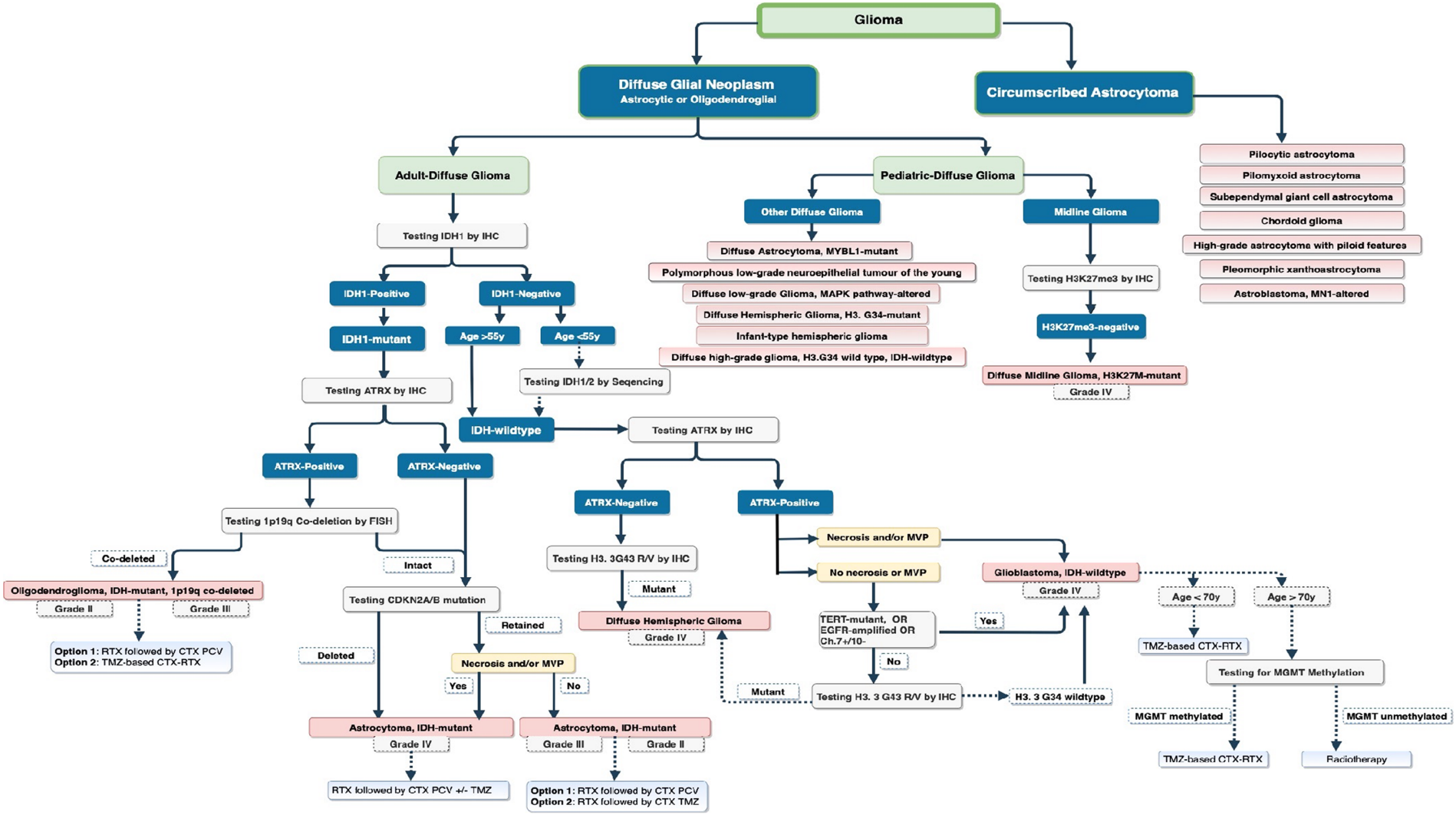

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Figure 1 A simple consensus approach to diagnose diffuse central nervous system gliomas using immunohistochemistry and molecular profiling, aided with the treatment strategy.

In this review, we presented a simple and practical diagnostic approach using histomolecular characteristics to define diffuse CNS gliomas accurately. We also associated the newly published 5th edition of the 2021 WHO classification with the current and updated European Association of Neuro-Oncology (EANO) treatment guidelines.

DISCUSSION

Before 2016, the classification of CNS tumors was established based on histological findings and immunohistochemical tests. Between 2016 and 2021, molecular biomarkers were incorporated into the diagnostic criteria to differentiate CNS tumors into clustered groups[7,9]. The current 5th edition of the 2021 WHO classification does not recommend a specific assessment method to identify molecular alterations unless a distinct tumor subtype is in the differential diagnosis. The cIMPACT-NOW has emphasized the confirmatory diagnosis of astrocytoma with the presence of *IDH* mutation or wild type, *ATRX* loss, *TP53* mutation, and lack of 1p/q19 codeletion[7,10]. In comparison, diffuse gliomas (classified as WHO grades 2 and 3) are either *IDH* wild type or *IDH1*$^{-}$ mutant[11,12]. As a key feature of oligodendroglioma, it, by definition, must harbor an *IDH* mutation and 1p/19q codeletion.

If *IDH1*^{R132H} is immunonegative in astrocytic or oligodendroglial tumors of WHO grades 2 and 3 or in patients aged less than 55 years, IDH1 (132 codon) and/or IDH2 (172 codon) Deoxyribonucleic acid (DNA) sequencing should be performed using the Sanger method or polymerase chain reaction (PCR) [13,14]. Otherwise, IDH1 immunonegative in patients aged greater than 55 years is likely to be IDH-wild type with an incidence rate of < 1% and acts like a high-grade glioma. Meanwhile, IDH1/2 DNA sequencing is preferable for detecting non-canonical mutations[15]. A non-canonical IDH mutation and a loss of ATRX mutation and O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation[7] have been associated with a family history of cancer and astrocytoma of the infratentorial region being identified at 80% of the time in multicentric astrocytoma[16].

ATRX mutation should also be tested in all gliomas, whether *IDH1/2* is a mutant or wild type. *ATRX* can be tested by immunohistochemistry (IHC). In oligodendroglioma, positive *ATRX*, negative *TP53*, and *TERT* mutations in *IDH*-mutant tumors are prevalent; nonetheless, 1p19q codeletion using fluorescence in situ hybridization (FISH) should be tested. However, false-positive results are expected to be less than 4% in most cases[17,18]. In both astrocytomas and oligodendrogliomas, the presence of homozygous deletion of *CDKN2A/B* at 9p21 is associated with poor prognosis in such groups, leading to decreased overall survival (OS)[11]. *CDKN2A/B* gene mutation can be tested through next-generation sequencing or the Sanger method if the tumor is *IDH*-mutant and 1p19q is not codeleted[19] (Figure 1). Loss of p16 expression (a marker of CDKNA/B) is associated with poor prognosis in *IDH*-mutant tumors and those with 1p/19q codeletion[20]. *CDKN2A/B* deletion is detected in both the wild-type and mutant *IDH*; however, it has been related to a reduction in OS in wild-type tumors[21-23].

Glioblastomas are routinely diagnosed based on histological findings of microvascular proliferation (MVP) and/or necrosis, and are molecularly defined as either *IDH*-mutant (10%) or *IDH*-wild-type (90%) tumors with significantly different biology and prognoses[8]. The terminology of *IDH*-mutant glioblastoma was omitted from the cIMPACT as they are biologically different from *IDH*-wild-type astrocytomas and were defined as *IDH*-mutant WHO grade 4 astrocytomas. Glioblastoma is referred to as *IDH*-wild-type glioblastoma or astrocytoma. There are no longer *IDH*-mutant glioblastomas. Another new terminology is an astrocytic glioma with *IDH* wild type, but with the presence of a histone 3 (H3) mutation, classified as a WHO grade 4 astrocytoma[9,24] (Figure 1). In glioblastoma, Telomerase reverse transcriptase (*TERT)* promoter mutations, Epidermal growth factor receptor (*EGFR)* mutations, and/or loss of chromosome 10 with gain of chromosome 7 are all prevalent[25]. If one of these features is detected, glioblastoma should be immediately diagnosed regardless of the presence of necrosis and/or MVP[26]. The presence of the H3F3A G34 histone mutation with chromosomal 1q gain distinguishes pediatric diffuse hemispheric glioma from adult diffuse hemispheric glioma. *EGFR*, *TERT*, *CDKNB2A/B*, and Ch10-Ch7+ are usually identified in adults; however, they should be tested for H3F3A gene mutation[27,28]. In comparison, the 2021 WHO classification has included *IDH* wild type and *H3F3A* in diffuse high-grade pediatric astrocytoma (most commonly from the pons in more than two-thirds of the cases, followed by the spinal cord and thalamus)[29].

H3-K27 is another commonly reported histone mutation in midline gliomas, ependymomas, and gangliogliomas[30-32]. Altered mitogen activated protein kinase (*MAPK)* pathway and *H3-K27*-mutant tumors are associated with diffuse low-grade midline gliomas and are associated with prolonged OS of more than 10 years[33]. The astroblastoma tumor is a new entity, *MN1*-altered, with better OS compared to C11Orf95-*RELA* and *BRAF*-positive astrocytic tumors[34]. Four other categories of diffuse astrocytomas were described in the 5th edition of the WHO classification, which included angiocentric gliomas, polymorphous low-grade neuroepithelial tumors of the young, and diffuse low-grade gliomas (*MAP* altered) (Figure 1). Infantile gliomas have a special genetic signature with fusion genes of *MET*, *ROS1*, *ALK*, or *NTRK1/2/3*[35,36].

Guidance to treatment modalities

A positive prognostic factors in diffuse gliomas include young patients, good Karnofsky performance status (KPS), total resection, and *MGMT* promoter methylation[37]. Surgical resection is considered the cornerstone of therapy, with a 5-year survival rate (80%) followed by watchful waiting in low-grade gliomas. However, total resection may result in neurological deficits; thus, awake craniotomy and imaging modalities, such as tractography, may be utilized on a case-by-case basis[38,39]. Postoperatively, MRI can detect residuals, and perfusion studies may detect progression[40]. Therefore, the care plan must be through a multidisciplinary approach with neurooncologists, neuropathologists, and neurosurgeons on board to discuss management modalities.

For low-grade gliomas, such as *IDH*-mutant and 1p/19q codeleted oligodendroglioma (WHO grade 2), careful, a watchful waiting strategy is an option, particularly for totally resected tumors or younger patients (< 40 years) with incomplete tumor resection. However, this would come at a cost: the patient's life, neurological impairments development, and a substantial increase in histological grading over time [41,42]. As a result, disease progression must be monitored with neuroimaging every 2–3 months. According to the National Comprehensive Cancer Network guidelines, patients should be followed up every 2 months with an MRI brain scan, then every 3 months if they have been off therapy for a year [40]. Progression may occur after 4–8 weeks, necessitating a brain MRI. Perfusion studies and spectroscopy can help to differentiate between progression and pseudoprogression, and, in doubt, a multidisciplinary team should be counseled.

Adjuvant radiotherapy

Post-surgical resection radiotherapy is the best therapeutic effect to prevent recurrence or delay the progression of diffuse gliomas (WHO grades 2-4)[43]. The role of radiotherapy is to maintain the control of tumor progression, but it leads to neurotoxicity if used in high doses. Thus, the most used doses are 50-60 Gy administered 3-5 times postoperatively[44]. Choi *et al*[45] found that patients with WHO grade 4 astrocytoma who received 50-60 Gy lived an average of 9 months longer than those who received 45 Gy for 3 months.

Radiotherapy is recommended for all WHO grade 2 gliomas with incomplete resection or for patients aged > 40 years and all WHO grade 3–4 gliomas. Early radiotherapy has been shown to prolong progression-free survival but not OS[46]. Whole-brain radiation therapy is usually not preferable in clinical practice because it is associated with cognitive effects[45]. A follow-up MRI 3-4 weeks after radiotherapy completion is typically performed to monitor disease progression[40]. The use of chemotherapy without radiation remains under investigation but might be an option if radiotherapy is not possible, for example, in patients with large tumors or elderly patients who might not be candidates for radiation.

Chemotherapy

Another adjunct treatment modality for diffuse gliomas is pharmacological treatment, mainly for patients with high-grade gliomas. The most used drug is the alkylating agent temozolomide (TMZ) for its immunomodulation and contribution to tumor-acquiring cell death. TMZ was first discovered in 1987 and has been widely applied as an effective first-line chemotherapeutic agent for treating patients with glioblastoma since the Food and Drug Administration has approved its efficacy in 2005[47,48]. Other drugs used as adjuvants in treating gliomas include nitrosourea, which includes lomustine, carmustine, nimustine, and fotemustine. However, this class of drugs may cause pronounced low platelet count when administered long-term. As a result, patients with oligodendroglioma frequently receive a procarbazine, vincristine, and lomustine (PCV) regimen, as dose-related side effects are more evident in other nitrosourea classes, such as gastrointestinal disorders, decreased cell count, and ototoxicity[48]. Anti-vascular endothelial growth factor antibody (bevacizumab) has also been used as an adjuvant treatment, but it's clear benefit is uncertain[49].

Recent update in glioma treatment

In the new 2021 WHO, cIMPACT-NOW, and EANO guidelines, therapeutic options are targeted at the genomic types of tumors[7,9]. As total surgical resection remains the standard treatment for all CNS gliomas, radiotherapy is still considered the first-line targeted therapy after surgical resection for all WHO grade 2 and 3 oligodendrogliomas or astrocytomas, as mentioned previously[50-52].

In patients with *IDH*-mutant oligodendroglioma (WHO grade 2 or 3) with 1p19q codeletion, aged > 40 years or with no totally resected tumor, and associated with comorbidities, residuals, or recurrence > 15 cm[3], radiotherapy followed by PCV chemotherapy regimen is recommended[51]. According to the two trials (EORTC 26951 and RTOG 9402), the combination of radiotherapy and PCV regimen showed a considerable benefit[52,53].

Radiotherapy followed by chemotherapy is recommended for all patients with *IDH*-mutant WHO grade 2, 3, or 4 astrocytomas, particularly in patients aged > 40 years, with incompletely resected tumors, and associated with neurological deficits[51]. TMZ is often preferred over PCV owing to its safety and ease of administration. However, radiotherapy followed by PCV constitutes the current standard of care for patients with *IDH*-mutant astrocytomas (WHO grade 2)[51]. The RTOG 9802 trial

reported a major prolongation of OS with the addition of PCV to radiotherapy, from 7 to 13 years in patients with WHO grade 2 gliomas who had undergone a subtotal resection or in those aged ≥ 40 years [54]. To prevent functional deficits, diffusion tensor imaging and functional MRI can be utilized[55]. In recurrence, repeat surgery with radiation and chemotherapy (TMZ and nitrosourea) can be considered equally efficient in treatment[9]. For *IDH*-mutant WHO grade 3 astrocytoma, the EORTC 26053 trial of radiotherapy alone, with concomitant or maintenance TMZ, showed a significant prolongation of OS in patients receiving radiotherapy followed by maintenance TMZ[56]. Therefore, TMZ chemotherapy is considered as the standard treatment for tumour progression after surgery and radiotherapy for most patients with *IDH*-mutant gliomas (WHO grade 2 or 3).

Glioblastoma (*IDH*-wild-type grade 4 astrocytoma) is best managed by gross total resection followed by radiotherapy[51]. In non-feasible or nearly total resection cases with age ≥ 70 years, radiotherapy (60 Gy in 30 fractions) or over fractionated radiotherapy (40 Gy in 15 fractions) is preferable to increase OS [9]. Higher survival rates are recorded in younger age groups < 65 years at diagnosis, with a median of up to 40 weeks. However, *TERT* mutation, gain of chromosome 7, and loss of chromosome 10 are associated with poor prognosis[57]. Neurocognitive outcomes can be affected by overfractionated radiotherapy. In patients with good KPS and aged < 70 years, a combination of radiotherapy and chemotherapy (TMZ) is the standard therapy[58]. Combined TMZ with lomustine in early diagnosis may increase OS, particularly in *MGMT*-methylated glioblastomas[59-61]. Hypofractionated radiotherapy is preferable for patients aged ≥ 70 years. The standard-of-care treatment for patients with recurrent glioblastoma has not yet been clarified; treatment is selected based on the prior therapy, patient's age, KPS score, MGMT promoter methylation status, and disease progression. Therefore, surgery and radiotherapy should be considered. Nitrosourea regimens, TMZ, with consideration of bevacizumab are options for pharmacotherapy but have an unconfirmed effect on OS. In patients who did not benefit from adjuvant radiotherapy or had an early symptomatic progression, a second surgery could be considered 6 months after the initial surgery aiming to increase OS[62].

There is a limitation of surgical management in *H3-K27M*-mutant diffuse midline glioma (WHO grade 4) because of its eloquent structures, including the pituitary, thalamus, midbrain, pons, and medulla, and it has a 5-year survival period of < 1%. Radiotherapy is often used but is associated with a poor prognosis. However, in hemispheric glioma, chemoradiotherapy drugs can be used because most of these tumors are *MGMT*-methylated[63].

CONCLUSION

In this review, we presented a simple diagnostic approach to differentiate diffuse CNS gliomas into molecularly defined subtypes using histomolecular features, based on the 5th edition of 2021 WHO classification of CNS tumors. This is to emphasize that molecular profiling is important in the diagnostic classification and grading of diffuse CNS gliomas. We also defined the role of different treatment modalities of surgery, radiotherapy, and pharmacotherapy in the treatment of these molecular defined gliomas. In fact, our review intends to serve as a simple reference for the diagnosis of CNS gliomas for healthcare providers.

FOOTNOTES

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