

子痫前期胎盘组织中神经型Wiskott-Aldrich综合征蛋白的表达及其意义

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摘要 目的 研究子痫前期胎盘组织中神经型Wiskott-Aldrich综合征蛋白(N-WASP)的表达情况及其临床意义。方法 选取2020年7月至2021年12月于中国医科大学附属盛京医院分娩的65例孕产妇作为研究对象,并将其分为早发型子痫前期组(15例)、早发对照组(15例)、晚发型子痫前期组(15例)、晚发对照组(20例)。采用实时定量PCR(RT-qPCR)检测各组胎盘组织中N-WASP mRNA的相对表达量,采用Western blotting和免疫组织化学法检测各组胎盘组织中N-WASP蛋白的表达情况及定位情况。结果 RT-qPCR、Western blotting结果显示,早发型子痫前期组胎盘组织N-WASP mRNA和蛋白表达水平显著低于早发对照组(0.50 ± 0.19 vs. 0.93 ± 0.73 , 0.35 ± 0.17 vs. 0.72 ± 0.21),晚发型子痫前期组胎盘组织中N-WASP mRNA和蛋白表达水平显著低于晚发对照组(0.83 ± 0.34 vs. 1.15 ± 0.34 , 0.39 ± 0.16 vs. 0.76 ± 0.20),差异均有统计学意义(均 $P < 0.05$)。N-WASP mRNA在胎盘组织中的表达与早发型及晚发型子痫前期的发生均呈负相关($r = -0.37, P = 0.042$; $r = -0.39, P = 0.019$)。免疫组织化学检测显示N-WASP蛋白定位于合体滋养细胞、细胞滋养细胞、绒毛间质细胞和血管内皮细胞的胞质中。结论 N-WASP低表达可能与子痫前期的发生密切相关。

关键词 神经型Wiskott-Aldrich综合征蛋白; 子痫前期; 滋养细胞

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Expression and significance of N-WASP in placentas with preeclampsia

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Abstract Objective To study the expression and clinical significance of neural Wiskott-Aldrich syndrome protein (N-WASP) in placentas with preeclampsia. **Methods** This study included a total of 65 pregnant women; 15 in the early-onset preeclampsia group, 15 in the early-onset control group, 15 in the late-onset preeclampsia group, and 20 in the late-onset control group. Real-time fluorescence quantitative PCR (RT-qPCR) was used to detect the relative expression of N-WASP mRNA in placental tissues. Western blotting and immunohistochemistry were used to detect the expression and position of N-WASP protein in placental tissues from each group. **Results** RT-qPCR revealed significantly lower N-WASP mRNA expression levels in the placental tissue of the early-onset preeclampsia group compared to those in the early-onset control group (0.50 ± 0.19 vs. 0.93 ± 0.73 , $P < 0.05$). The N-WASP mRNA expression levels in late-onset preeclampsia placenta were significantly lower than those in the late-onset control group (0.83 ± 0.34 vs. 1.15 ± 0.34 , $P < 0.05$). Western blotting revealed significantly lower N-WASP protein expression in the placental tissue of early-onset preeclampsia compared to that in the early-onset control group (0.35 ± 0.17 vs. 0.72 ± 0.21 , $P < 0.05$). The N-WASP protein expression in late-onset preeclampsia placenta was significantly lower than that in the late-onset control group (0.39 ± 0.16 vs. 0.76 ± 0.20 , $P < 0.05$). The N-WASP mRNA expression in the placenta negatively correlated with the occurrence of early-onset ($r = -0.37, P = 0.042$) and late-onset preeclampsia ($r = -0.39, P = 0.019$). Immunohistochemistry revealed that N-WASP protein was localized in the cytoplasm of syncytiotrophoblasts, cytotrophoblasts, villous stromal cells, and vascular endothelial cells. **Conclusion** The low expression of N-WASP may be closely associated with preeclampsia.

Keywords neural Wiskott-Aldrich syndrome protein; preeclampsia; trophoblast

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子痫前期是最常见的妊娠期特发性疾病,其发生是一个多因素、多步骤、多环节的过程,涉及多器官损伤,不仅增加了孕产妇及围产儿的死亡率和发病率,而且与糖尿病、心血管和肾脏相关疾病等的远期不良预后有关^[1]。目前普遍认为胎盘在子痫前期的发病中发挥着至关重要的作用^[2]。滋养细胞的迁移和侵袭能力不足,子宫螺旋动脉出现重塑障碍^[3],合体滋养细胞功能异常^[4],均可影响胎盘正常发育,导致子痫前期的发生。

神经型Wiskott-Aldrich综合征蛋白(neural Wiskott-Aldrich syndrome protein, N-WASP)是由位于7q31.32的WASL基因编码而成,分子量 65×10^3 。N-WASP作为一种成核促进因子^[5],能够调控肌动蛋白丝成核的程度、速度和位置,通过细胞骨架的重排参与组织形态的发生、细胞的侵袭和迁移等多种生物学行为。研究^[6-7]发现,N-WASP在肿瘤的侵袭和转移、胚胎的发育及细胞-细胞融合的过程中起重要作用。本研究通过检测子痫前期胎盘组织中N-WASP的表达情况,探讨其在子痫前期发病中的作用,以期为子痫前期的早期诊断和治疗提供新的思路和方法。

1 材料与方法

1.1 研究对象

选取2020年7月至2021年12月间在中国医科大学附属盛京医院产科病房分娩的孕产妇65例作为研究对象,均为单胎妊娠,胎儿无发育异常,病理未见绒毛膜羊膜炎,均排除原发性高血压、糖尿病、慢性肾炎等病史。子痫前期诊断标准参照中华医学会妇产科学分会妊娠期高血压疾病学组发布的《妊娠期高血压疾病诊治指南(2020)》^[8]。分组:(1)子痫前期组,共30例,进一步分为早发型子痫前期(early-onset preeclampsia, EOPE)组(分娩孕周 <34 周, $n=15$)和晚发型子痫前期(late-onset preeclampsia, LOPE)组(分娩孕周为 $34\sim 40$ 周, $n=15$);(2)正常对照组,共35例,匹配早发型及晚发型子痫前期组孕妇年龄及分娩孕周,进一步分为早发对照组(ENC组,分娩孕周 <34 周, $n=15$)和晚发对照组(LNC组,分娩孕周 $34\sim 40$ 周, $n=20$)。本研究已获得中国医科大学附属盛京医院医学伦理委员会伦理审查批准(伦理编号2021PS890K)。所有研究对象及其家属均知情同意。

1.2 研究方法

1.2.1 标本的收集和处理:胎盘娩出5 min内,术者自胎盘4象限中点处各取一块 $1 \text{ cm} \times 1 \text{ cm}$ 全层胎盘组织,取材时避开胎盘大血管、边缘、钙化及坏死组织。于生理盐水中反复清洗,尽量洗净胎盘绒毛中的血液,用无菌滤纸吸干水分,取部分组织置于无菌冻存管并迅速转移至液氮罐内, $-80 \text{ }^\circ\text{C}$ 冻存备用。其余胎盘组织在洗去胎盘绒毛中血液后,4%多聚甲醛固定,以备石蜡包埋用。

1.2.2 免疫组织化学染色:取出4%多聚甲醛溶液中固定的胎盘组织,石蜡包埋,切片(厚 $3\sim 4 \mu\text{m}$)。采用试剂盒(KIT-9710,福州迈新生物技术开发有限公司)行免疫组织化学染色,严格按照说明书操作。用PBS稀释兔抗人WASL多克隆抗体(英国PROTEINTECH公司)至 $1:100$,用PBS替代一抗作为阴性对照。用DAB显色试剂盒(DAB-0031,福州迈新生物技术开发有限公司)进行显色,于光学显微镜下观察胎盘组织出现棕黄色染色时为阳性。苏木素复染细胞核5 min。应用NIS-Elements软件进行图像采集和分析。

1.2.3 实时定量聚合酶链反应(quantitative real-time polymerase chain reaction, RT-qPCR)检测胎盘组织中N-WASP mRNA表达水平:取约60 mg胎盘组织,采用TRIzol法提取总RNA,检测RNA浓度后,按Perfect Start[®] Uni RT&qPCR Kit(北京全式金生物技术股份有限公司)说明书逆转录成cDNA。引物(上海生工生物有限公司设计并合成)序列:WASL,正向 $5' \text{-GC TCTGGACGAGATGCACTGTTAG-3'}$,反向 $5' \text{-CAGGT GTTGCTGCTAGACTCTTG-3'}$;以18S作为内参照,正向 $5' \text{-ATCCTCAGTGAGTTCTCCCG-3'}$,反向 $5' \text{-CT TTGCCATCACTGCCATTA-3'}$ 。PCR体系按Perfect Start[®] Green qPCR SuperMix(北京全式金生物技术股份有限公司)说明书配制,于PCR仪中行扩增检测:94 $^\circ\text{C}$ 30 s预变性;94 $^\circ\text{C}$ 5 s,60 $^\circ\text{C}$ 30 s,40个循环。分析溶解曲线,通过循环阈值(cycle threshold, Ct),采用 $2^{-\Delta\Delta\text{Ct}}$ 法计算mRNA相对表达水平。每个样本设3个复孔,重复实验3次。

1.2.4 Western blotting:取约100 mg胎盘组织提取蛋白,用Omni-Easy[™]即用型BCA蛋白定量试剂盒(上海雅酶生物医药科技有限公司)检测浓度,并调整蛋白上样量。凝胶恒压电泳(150 V,75 min),转膜

70 min, 用5%脱脂奶粉室温缓慢摇匀封闭4 h, 加入兔抗人WASP多克隆抗体(1 : 2 000, 英国PROTEINTECH 公司)、兔抗人GAPDH多克隆抗体(1 : 3 000, 英国PROTEINTECH 公司), 4 ℃孵育 16 h。次日室温复温 30 min。加入辣根过氧化物酶标记的山羊抗兔二抗孵育液(1 : 5 000, 北京中杉金桥公司), 室温摇床孵育2 h。用增强显影液凝胶成像仪曝光成像。用Image Lab软件检测目的蛋白与内参照条带灰度值比值, 分析目的蛋白相对表达量。

1.3 统计学分析

采用SPSS 26.0和GraphPad Prism 9.0软件进行统计学分析。计量资料用 $\bar{x} \pm s$ 表示。若2组数据满足正态分布, 当两总体方差齐时, 两样本均数比较采用 t

检验; 当两总体方差不齐时, 采用 t 检验(Satterthwaite法)比较。若2组数据不满足正态分布, 两样本均数比较采用 Mann-Whitney U 检验。计数资料采用非参数 χ^2 检验进行比较。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 各组一般情况比较

与相应的正常对照组比较, EOPE组及LOPE组年龄及分娩孕周无统计学差异($P > 0.05$), 收缩压、舒张压、24 h尿蛋白定量均显著升高, 新生儿出生体重显著降低, 差异均有统计学意义(均 $P < 0.05$)。见表1。

2.2 N-WASP在胎盘组织中的定位及各组胎盘组织

表1 各组研究对象一般情况($\bar{x} \pm s$)
Tab.1 Basic data of each group ($\bar{x} \pm s$)

Group	<i>n</i>	Age (year)	Gestational week (week)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	24 h urinary protein quantity (g)	Neonatal birth weight (g)
EOPE	15	32.53 ± 3.82	31.47 ± 2.76	150.31 ± 25.22 ¹⁾	96.47 ± 14.37 ¹⁾	7.81 ± 5.20 ¹⁾	1 784 ± 280 ¹⁾
ENC	15	31.41 ± 3.96	31.64 ± 2.31	117.86 ± 11.51	79.82 ± 9.75	0.07 ± 0.05	2 002 ± 152
LOPE	15	30.54 ± 4.01	37.76 ± 1.54	154.63 ± 16.52 ²⁾	104.39 ± 11.24 ²⁾	6.32 ± 3.47 ²⁾	2 875 ± 528 ²⁾
LNC	20	31.75 ± 4.13	38.43 ± 1.44	120.83 ± 7.36	72.30 ± 8.76	0.08 ± 0.03	3 463 ± 713

1) $P < 0.05$ vs. group ENC; 2) $P < 0.05$ vs. group LNC. EOPE, early-onset preeclampsia; ENC, early-onset control; LOPE, late-onset preeclampsia; LNC, late-onset control.

的HE染色

免疫组织化学染色结果显示, 子痫前期胎盘组织及正常对照组胎盘组织中均可见N-WASP表达, EOPE和LOPE胎盘组织中阳性染色较对应的正常对照组明显减弱。N-WASP在细胞质中表达, 主要定位于合体滋养细胞、细胞滋养细胞。HE染色结果显示正常对照组胎盘组织绒毛滋养层饱满, 而子痫前期胎盘组织中滋养细胞层明显变薄, 部分不均匀。见图1。

2.3 各组胎盘组织中N-WASP mRNA表达水平比较

RT-qPCR结果显示, EOPE组胎盘组织中N-WASP mRNA表达水平低于ENC组(0.50 ± 0.19 vs. 0.93 ± 0.73), 差异有统计学意义($P < 0.05$)。LOPE组胎盘组织中N-WASP mRNA表达水平也显著低于LNC组(0.83 ± 0.34 vs. 1.15 ± 0.34), 差异有统计学意义($P < 0.05$)。见图2。N-WASP mRNA在胎盘组织中的表达与EOPE的发生呈负相关($r = -0.37, P = 0.042$); 与LOPE的发

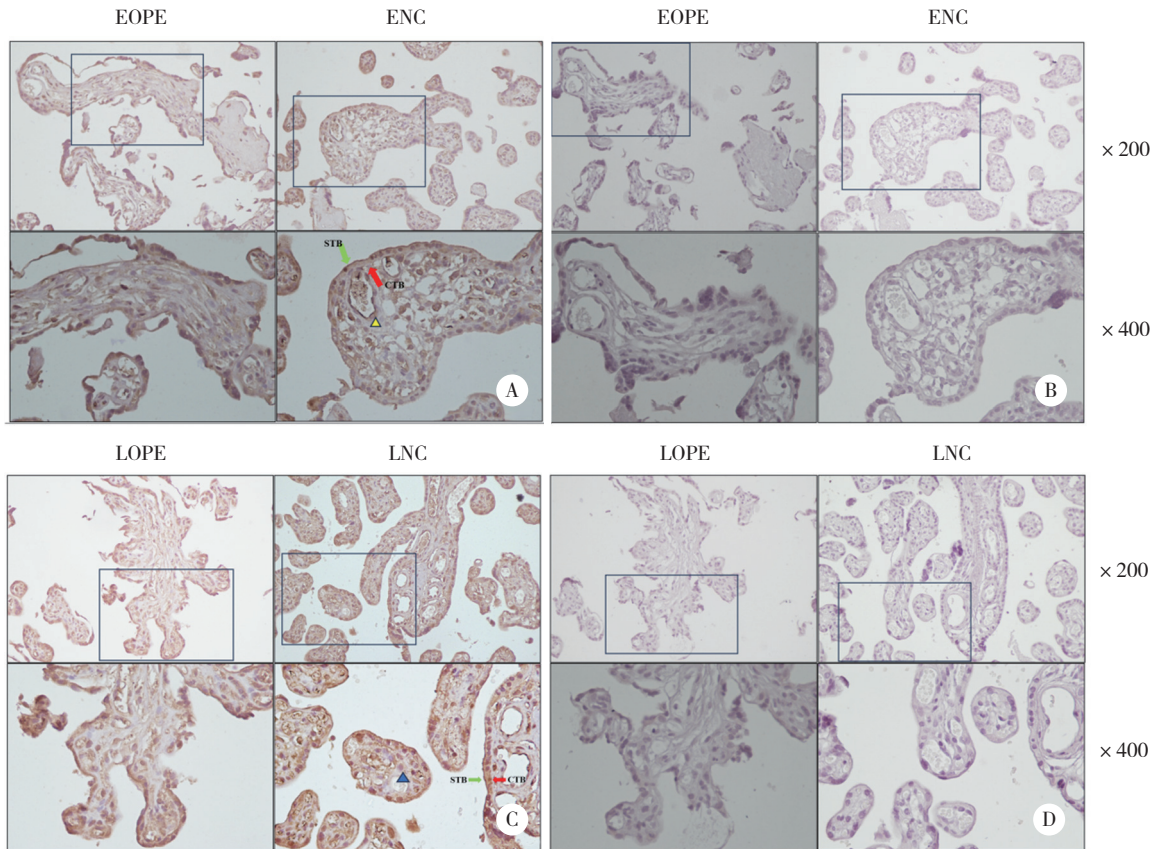
生同样呈负相关($r = -0.39, P = 0.019$)。

2.4 各组胎盘组织中N-WASP蛋白表达水平比较

Western blotting结果显示, EOPE组胎盘组织中N-WASP蛋白表达低于ENC组(0.35 ± 0.17 vs. 0.72 ± 0.21), 差异有统计学意义($P < 0.05$); LOPE组胎盘组织中N-WASP蛋白表达也显著低于LNC组(0.39 ± 0.16 vs. 0.76 ± 0.20), 差异有统计学意义($P < 0.05$)。见图3。

3 讨论

子痫前期是妊娠期特有的疾病, 严重影响母婴健康, 是孕产妇和围产儿病死率升高的主要原因之一^[9]。胎盘在子痫前期的发病机制中发挥着至关重要的作用。在妊娠早期, 绒毛外滋养细胞能穿透蜕膜浸润至子宫肌层, 进而重塑子宫螺旋动脉, 形成高排低阻状态, 建立起有效的子宫-胎盘循环^[10]。滋养细胞浸润过浅, 子宫螺旋动脉重塑不足, 子宫-胎



A, expression of N-WASP protein in EOPE and ENC groups; B, HE staining of placenta tissue in EOPE and ENC groups; C, expression of N-WASP protein in LOPE and LNC groups; D, HE staining of placenta tissue in LOPE and LNC groups. STB, syncytiotrophoblast; CTB, cytotrophoblast; yellow triangle, vascular endothelial cell; blue triangle, villous interstitial cell.

图1 胎盘组织中N-WASP定位表达及各组胎盘组织HE染色

Fig.1 Localization of N-WASP in different placental tissues by immunohistochemical staining and HE staining of placental tissues in different groups

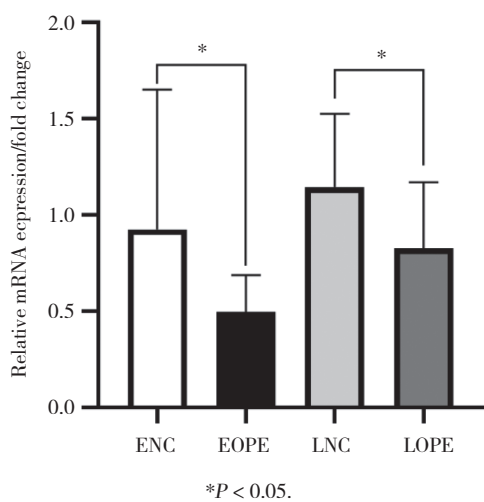


图2 各组胎盘组织中N-WASP mRNA表达水平

Fig.2 N-WASP mRNA expression levels in different placental tissues

盘循环无法有效建立,均可导致子痫前期发生。此外,胎盘细胞滋养细胞分化融合形成合体滋养细

胞层,对于胎盘的形成功能同样至关重要。合体滋养细胞层作为母胎界面屏障参与并维持了胎盘正常功能^[11]。研究^[4,12]发现,当滋养细胞合体化不足、合体滋养细胞功能障碍,子痫前期胎盘组织于显微镜下呈现合体滋养层形态学异常改变,表现为合体滋养层变薄、不连续,以及出现多个液泡。同时,当滋养细胞合体化异常时也会引发子痫前期^[13]。本研究中同样也观察到上述情况,与正常对照组胎盘组织相比,子痫前期组胎盘组织滋养层变薄,合体滋养层部分不均匀,甚至出现不连续。

N-WASP作为肌动蛋白调节蛋白,能够调控细胞骨架的重排,参与丝状伪足、侵袭性伪足以及伪足小体的形成^[14]。这些生物学行为影响了细胞在间质中运动所必需的迁移和侵袭能力。N-WASP作为肌动蛋白细胞骨架的调控网络中心,参与了多种肿瘤细胞的侵袭及转移。在宫颈癌组织及细胞系

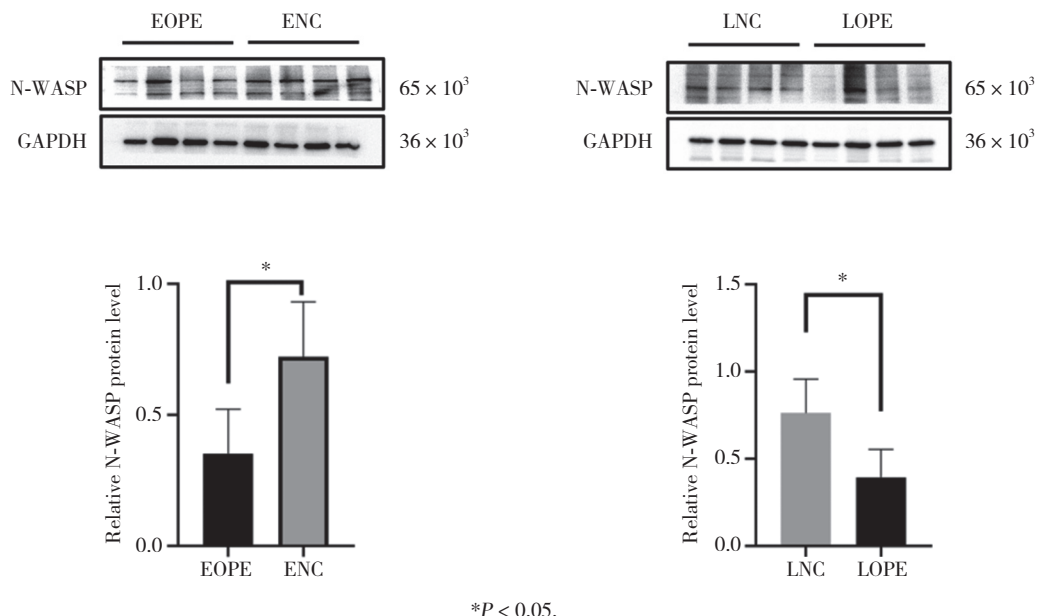


图3 胎盘组织中N-WASP 蛋白表达水平

Fig.3 N-WASP protein expression levels in different placental tissues

中,均发现N-WASP呈过表达并促进了宫颈癌细胞的迁移和侵袭能力^[15]。胞外-5'-核苷酸酶通过腺苷A1受体诱导N-WASP发生构象变化,调节细胞间的黏附和肌动蛋白聚合,在正常组织中对上皮完整性起到了保护作用,而子宫内膜癌中这一平衡遭到破坏,导致肿瘤进展^[16]。N-WASP在不同肿瘤组织中表达情况不同,N-WASP高表达与胰腺癌^[17]、肝癌^[18]、食管鳞状上皮癌^[19]和乳腺浸润性导管癌^[20]的不良预后和生存率呈负相关^[17-18,21],而在肾透明细胞癌中则表达水平降低^[21],提示其表达具有组织特异性,且其表达水平的改变对细胞的侵袭和迁移能力有直接的影响。另有研究^[6]发现,WASP的果蝇同系物W_{Sp}是幼年及成年果蝇成肌细胞融合的重要促进剂。在小鼠胚胎发育中,N-WASP功能被破坏时,小鼠胚胎的成肌细胞无法融合^[7]。目前尚无关于N-WASP在滋养细胞中表达情况及其与子痫前期发生关系的相关研究。

本研究发现,N-WASP在胎盘滋养细胞及合体滋养细胞中均有表达,早发型及晚发型子痫前期胎盘组织中N-WASP mRNA及蛋白表达水平均明显低于对应的正常对照组,同时N-WASP mRNA在胎盘组织中的表达与子痫前期的发生呈负相关。因此,推测N-WASP通过调节肌动蛋白或通过影响肌动蛋白相关蛋白的表达水平导致细胞骨架的重排,从而

对滋养细胞的迁移及浸润能力产生影响,致使子宫螺旋小动脉重塑障碍;此外,N-WASP也可能通过影响滋养细胞合体化的过程参与了子痫前期的发生。综上所述,N-WASP在子痫前期胎盘组织中低表达,其表达情况与子痫前期的发生密切相关。

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