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·综述·

疱疹性咽峡炎与手足口病的相关性研究进展

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【摘要】 疱疹性咽峡炎（herpangina，HA）与手足口病（hand-foot-mouth disease，HFMD）均是由肠道病毒感染引起的急性传染性疾病，在许多方面都有相似之处。首先，二者感染源高度重合，且不同地区流行株之间VP1区域序列无明显差异，同源性较高。其次，二者流行特征有许多相似之处：均以夏季多发、易感人群均为低年龄段婴幼儿。同时在临床表现与预后方面，两者也有一定的相关性：HA临床表现为咽峡与软腭处的疱疹及溃疡，伴有发热、喉痛与食欲减退，预后较好；HFMD临床表现为口腔颊、舌黏膜处溃疡，与手部、足部、膝部与臀部的特征性水疱，可出现重症型。一方面，虽然多数HA具有自限性且预后良好，但有文献表明具有特定临床表现如腹泻、呕吐、肢体抖动、嗜睡的HA有可能进展为HFMD，另一方面，早期出现的HA是重症HFMD的危险因素，重症HFMD甚至仅表现为口腔咽峡部疱疹。医护人员应重视对HA临床表现的观察，尽早识别潜在的HFMD患儿，防止其进一步发展或转化。

【关键词】 疱疹性咽峡炎；　手足口病；　肠道病毒；　传染病；　自限性疾病；
婴幼儿；　流行特征；　关联性

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Research progress on the correlation between herpangina and hand-foot-mouth disease

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【Abstract】 As acute enterovirus-induced infections, herpangina(HA) and hand-foot-mouth disease(HFMD) are similar in many aspects. Although these diseases vary with time and region, many studies have shown that the viruses causing HA and HFMD are consistent, and there is no notable difference in partial VP1 gene sequences between different viruses. HA and HFMD also resemble each other in epidemiological features. Both infections show significant summertime seasonality, have a strong connection with certain environmental conditions and are most prevalent in young children and infants. Herpangina is thought to be a mild disease, defined as vesicular enanthem and then ulcers of the fauces and soft palate with presentation of fever, sore throat, and decreased appetite. HFMD, which could lead to severe symptoms, is also characterized by oral ulcers, although they are chiefly on the buccal mucosa and tongue, and typical vesicular rashes, which are most commonly found on the hands, feet, knees and buttocks. While HA is generally believed to be self-limited and has a favorable prognosis, HA with certain clinical characteristics, such as diarrhea, vomiting, limb jitter and sleepiness, can evolve into HFMD, according to some literature in recent years. However, HA is an independent risk factor for HFMD, and severe cases only present with herpes appearing at the isthmus of the fauces at an early stage, which indicates a strong correlation between them. Clinical manifestations of HA should be considered by medical staff to identify potential children with HFMD as early as possible to prevent its further development or

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transformation.

【Key words】 herpangina; hand-foot-mouth disease; enterovirus; infection disease; self-limited disease; infant; epidemiological features; correlation
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疱疹性咽峡炎(herpangina,HA)与手足口病(hand-foot-mouth disease,HFMD)均是临床常见的小儿病毒感染性疾病。HA临床表现为骤起发热和口腔咽峡部疱疹,多数具有自限性,预后较好;少数重症病例进展迅速,会出现高热惊厥、脑炎等并发症,留下严重后遗症甚至导致死亡。HFMD大多数患者症状轻微,主要表现为手、足、臀部等离心性分布的皮疹及口腔疱疹;部分重症病例早期可仅表现为HA,临床上有时难以区分;少数患者可出现无菌性脑膜炎、脑炎、肺水肿及心肺功能衰竭,甚至导致死亡。同为肠道病毒感染性疾病,HA与HFMD二者在发病机制、临床特征及预后上有一定相似性,相较于对HFMD的大量研究,临床对HA重视程度不足,尤其是在疾病防控方面,也缺乏对其与HFMD关联性的系统探讨,笔者从病原体组成、流行特征、临床表现、联合防治等方面对HA与HFMD的关联性作一综述,以期为二者的联合防治提供新的思路。

1　病原学

HA与HFMD都可由多种肠道病毒感染引起,病原菌谱高度重合[1]。Ogi等[2]的研究表明,CVA6是日本库兵县HA与HFMD发病的主要病原体。Yao等[3]对161例HFMD和95例HA患者取样并检测,发现两病的主要病原体均为EV71。在中国台湾地区,CVA6分别在2009年与2010年引起HA与HFMD的流行,但Chen等[4]发现,这两年的流行株在VP1序列上并无显著差异。曾汉日等[5]于2015年对广州123例HA进行病毒学检测,发现主要引起当地HA疫情的CVA6病毒株与2015年及2013年引起广东省HFMD疫情的CVA6流行株在系统进化树中处于同一分支,同源性高。

HA与HFMD的重症病例主要由EV71引起。Li等[6]对2013~2015年北京HFMD患者的报道中,6例死亡患者中的5例都检测出EV71感染。Kim等[7]进行的横断面研究表明,EV71是2009~2012年间HA与HFMD重症病例的主要病原体。刘牧等[8]将发展为HFMD的HA患者与单纯HA患者进行对比则发现,部分EV71感染的HA患者更容易发展为重症HFMD,甚至可继发脑炎、肺水肿、循环障碍等而导致死亡。

上述临床研究表明HA与HFMD在病原学上存在关联性,但要进一步确证还需要进行大样本的前瞻性队列研究,通过长期观察追踪病变的发展过程予以证实。

2　流行病学特征

HA和HFMD在流行特征方面存在明显的相似性。首先,两者易感人群相似,均好发于1~2岁的低龄儿童[9-10]。Yang等[11]对2000~2012年中国台湾地区肠道病毒感染病例进行的追踪观察显示,HA与HFMD均更好发于男性。其次,HA与HFMD均好发于夏季[9],有学者[12]通过建立季节性气候模型进行分析后发现,特定气象条件如高温、高湿度、低降水量与短日照时间会使HA与HFMD发病率上升,这可能与肠道病毒在上述气温条件下增殖更活跃、性质更稳定有关。

综合以上研究可发现,HA与HFMD的发病特征方面有许多相似之处,但要完全确定二者之间的关联性尚需更多大范围流行病学调查结果支持。

3　临床表现

HA与HFMD存在相互转化的可能。有学者[13]对深圳市2008~2012年重症HFMD的临床与特征进行分析,发现重症患者手、足部皮疹出疹率逐年下降,而口腔疱疹出疹率呈明显增高趋势。Yao等[3]对HA和HFMD的对照研究表明,部分HA病例发热的比率要显著高于HFMD,且平均发热温度较高,说明这些患者神经系统受累程度较重,病情可能进一步恶化。刘牧等[8]将80例早期诊断为HA的患儿根据病情进展分为3组进行病例对照研究,发现相较于单纯HA患儿,进展为HFMD的HA患儿发热热程更长,热度更高,心率、血压、呼吸变化更明显,且症状严重程度与HFMD病情严重程度呈正相关。此外,HA患儿如出现食欲欠佳、腹

泻、呕吐、肢体抖动、嗜睡等症状，不但容易发展为HFMD，同时其病情一般较重，多在短期内发展为危重症HFMD。

一些共同的临床表现，如嗜睡、低龄、高血糖症等，对重症HFMD与HA的出现具有提示意义[14-15]。许多研究进一步表明，早期出现的HA对重症HFMD也有重要提示意义。Wang等[16]对商丘市重症与轻症HFMD各60例进行病例对照研究后发现，近一半的重症病例早期出现咽峡部疱疹，而这一比例在轻症HFMD中仅为23.7%。Chang等[17]将重症HFMD的临床表现分为4个阶段，其中第一个阶段就是手、足及口腔咽峡等部位的斑丘疹与疱疹，说明HA在某些条件下即是HFMD的始发表现，可以视为HFMD首发症状。该分级已被大量文献引用，并对治疗重症HFMD有一定的指导意义，我国2011年卫生部组织的重症EV71感染临床救治专家共识也参考了这一分期[18]。

除上述关联以外，HA与HFMD均可对机体免疫功能造成影响。Lee等[19]的研究发现HA患儿日后发生变应性鼻炎与异位性皮肤炎的几率增大，巴西也曾报道一例伴发类风湿性关节炎的HFMD患者[20]。Wang等[21]基于对中国台湾地区1997～2013年EV感染病例的研究也提出，EV感染会提高哮喘发病几率。以上证据说明免疫因素在HA转变为HFMD中可能具有重要作用，或为二者联系的基础。

尽管上述研究表明HA与HFMD密切相关，但尚不清楚二者之间是直接的因果关系还是相互促进关系，今后需要更多干预性试验来阐明HA治疗是否有利于预防HFMD。

4 防 治

患者与隐性感染者是HA与HFMD的主要传染源，故流行期应避免接触已确诊的患者。干净的饮用水有助于降低EV71感染风险[22]；Huang等[23]对中国台湾地区399名EV71感染患者的研究发现如果洗手后不经常清洗水龙头，严重EV71感染的OR值上升至2.63，提示经常清洗水龙头、保证饮用水的清洁是隔绝病毒传播的重要预防措施。

目前对HA与HFMD尚无特效疗法，缺乏特异性强且高效稳定的抗病毒药物，临床以对症治疗为主。目前针对EV感染的特异性抗病毒疗法尚在研究当中，Wang等[24]的研究认为EV71疫苗可显著降低EV71感染患儿的死亡率，建议将其纳入儿童基础接种疫苗范围。EV71/CVA16联合疫苗在临床研究中也已取得进展，研发中的疫苗包括以Vero细胞和二倍体细胞为基质的全病毒灭活疫苗、应用重组表达系统等，临床前动物模型均显示对同源和异源Cox A16毒株的保护作用[25]，有望改善HFMD和HA重症病例比率及降低病死率。

5 小 结

综上所述，HA与HFMD的感染病原谱高度重合并具有同源性，且EV71导致的HA更易进展为重症HFMD；二者的流行特征也相似，均好发于夏季与低龄人群，提示应改变以往仅针对单一疾病或单一病原的监测模式，在流行期将HA纳入HFMD的监测与防治，统筹防控，避免不同疾病的患者出现交叉感染。此外，有特定临床表现的HA进一步发展为HFMD的可能性更大，在某些情况下HA本身就是重症HFMD的危险因素或首发阶段，故医护人员应重视对HA临床表现的观察，尽早识别潜在的HFMD患儿，防止其进一步发展。

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