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脑性耗盐综合征的诊断与治疗进展

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脑性耗盐综合征(cerebral salt wasting syndrome, CSWS)由Peters于1950年首次报道,由急慢性中枢神经系统疾病导致的下丘脑–肾脏钠水调节功能紊乱,引起以低钠血症、尿钠排出增多、尿量增加、低血

容量、脱水表现和对补充血容量和钠盐治疗有效的综合征^[1]。血清房钠肽和(或)脑钠肽浓度升高是可能的致病机制,常见于脑手术、脑外伤、脑肿瘤、自主神经功能紊乱、脑膜炎及脑炎^[2-4]。CSWS、抗利尿激素不适当分泌综合征(syndrome of inappropriate antidiuretic hormone, SIADH)、医源性补充低张液体是成人

危重神经病常见导致低钠血症的原因,明确导致CSWS的原发病、诊断与治疗有助于提高我们临床医师对该病的认识^[1]。

一、脑性耗盐综合征的诊断标准

CSWS的特征是低血容量性低钠血症伴有多尿和尿钠增多,推荐CSWS的诊断标准为:①低钠血症<135mmol/L;②血浆渗透压<280mOsm/kg;③尿钠>40mmol/L;④至少以下两条:液体失衡≥-500ml/24h;体重下降≥500g/24h;血清尿素氮/肌酐≥20;24h内血细胞容积升高>3%;肺动脉楔压<18mmHg,中心静脉压<12mmHg^[1]。Nakagawa等^[2]指出以肾脏钠盐转运异常导致的细胞外液体积剥夺、低钠血症,而肾上腺和甲状腺功能正常为主要表现的患者可能是肾性耗盐综合征(renal salt-wasting syndrome,RSWS)。Bettinelli等^[3]通过对110例18岁以下的RSWS研究发现,导致RSWS的常见原因是颅内手术、脑膜脑炎和头部外伤,CWS的诊断需要动脉血容量减少的依据,而该依据常难以通过测量获得。因此,CSWS的诊断标准目前尚未被广泛认可的原因可能主要为目前尚缺乏诊断标准的特异性、敏感度研究,其次为未突出CSWS合并有急慢性中枢神经系统疾病的必要性,不能将CSWS与RSWS相鉴别有关^[3]。

二、脑性耗盐综合征与原发病及治疗进展

1. 脑性耗盐综合征与蛛网膜下腔出血:Kao等^[4]发现316例动脉瘤性蛛网膜下腔出血低钠血症发生率为59.2%(187/316),中到重度低钠血症发生率为15.2%(48/316),其中CSWS发生率为22.9%(11/48)。Nakagawa等^[5]研究发现39例蛛网膜下腔出血患者低钠血症发生率为28.2%(11/39),11例发生低钠血症的蛛网膜下腔出血组较正常血钠浓度组患者血清房钠肽浓度在蛛网膜下腔出血1~3天明显升高,其中45.5%(5/11)出现延迟的缺血性神经功能缺损(delayed ischemic neurological deficit,DIND),而正常血钠浓度组患者DIND发生率为7.1%(2/28),说明蛛网膜下腔出血后血清房钠肽浓度升高可能与低钠血症有关,并且,低钠血症可能增加蛛网膜下腔出血患者DIND发生率。因此,蛛网膜下腔出现并发CSWS的发生率虽然偏低,但是CSWS所引起的严重的低钠血症、水分丢失会严重影响患者预后。并且,在蛛网膜下腔出血低钠血症出现之前就应该开始补充钠盐和液体,而采用氟氢考的松有助于患者内环境的稳定,抑制尿钠分泌增多,从而有利于预防DIND

等严重并发症。

2. 脑性耗盐综合征与脑手术:Cardoso等^[6]研究了30例接受脑肿瘤切除(19/30)、脑动脉瘤夹闭术(11/30)后低钠血症病因,发现90%(27/30)的患者发生CSWS,其中46.7%(14/27)的患者血清精氨酸血管加压素减少,10%(3/30)的患者发生SIADH,并且接受脑肿瘤切除术组与脑动脉瘤夹闭术组CSWS的发病率无统计学差异。Sherlock等^[7]研究显示神经外科术后发生低钠血症的患者垂体病变[6.25%(5/81),P=0.004],外伤性脑损伤[9.6%(44/457),P<0.001],颅内肿瘤[15.8%(56/355),P<0.001],蛛网膜下腔出血[19.6%(62/316),P<0.001]较脊髓病变0.81%(4/489)患者多见,导致低钠血症的并发症中SIADH、CSWS、SIADH/CSWS同时存在分别为62%(116/187)、4.8%(9/187)、2.7%(5/187)。孙飞等^[8]研究发现68例鞍区病变手术患者中有30.9%(21/68)发生中枢性低钠血症,其中90.5%(19/21)诊断为CSWS,9.5%(2/21)诊断为SIADH。Ruiz-Juretschke等^[9]通过研究2例脑桥小脑脚的肿瘤术后并发CSWS的研究发现脑室外引流缓解继发性阻塞性脑积水可能是颅窝肿瘤手术治疗后并发SCWS的重要的治疗方法。Hardesty等^[10]对接受过291次经颅脑肿瘤切除术的282例患者研究发现,术后5%(15/282)患者发生CSWS,比SIADH发生率3%(9/282)更高,CSWS多于术后第3天出现,平均持续时间中位数为2.5天,患有CSWS的患者更容易罹患术后卒中,47%的CSWS患者发生低钠血症性癫痫。因此,脑手术后CSWS导致的低钠血症明显增加患者术后脑卒中、癫痫发生率,而及时补充过度丢失的血钠及水分,缓解继发性阻塞性脑积水等可能有助于治疗CSWS。CSWS在脑手术后发病率的高低明显存在争议的原因可能与CSWS及SIADH的鉴别水平的高低有关。

3. 脑性耗盐综合征与脑外伤:Lohani等^[11]研究33例脑外伤患者发现其低钠血症发生率为27.2%(9/33),其中33.3%(3/9)患者因CSWS导致中心静脉压下降,55.6%(5/9)患者因SIADH引起中心静脉压升高,指出尿酸排除率(fractional excretion of uric acid,FEUA)测量可能不足以区分CSWS和SIADH,而中心静脉压的高低对鉴别SIADH和CSWS有指导意义。Costa等^[12]研究发现26例脑外伤患者中出现34.6%(9/26)低钠血症,并且其负水平衡、尿排钠排钾、尿量较正常血钠浓度患者组多,指出血清中脑钠肽、醛固酮、血管加压素水平与CSWS血清钠离子浓

度降低无明显相关性。Katsuno 等^[13]报道了 2 例合并有头部外伤和脑梗死后表现为 CSWS 和脑动脉痉挛的患者,认为下丘脑周围静脉充血导致下丘脑功能紊乱是 CSWS 和外伤性脑动脉痉挛的原因。因此,脑外伤患者的研究指出 CSWS 患者存在的中心静脉压降低,负水平衡、尿排钠排钾、尿量增多的临床特点有助于鉴别 SIADH,但是目前尚无充分依据证明血清中脑钠肽、醛固酮、血管加压素水平降低与 CSWS 有关。

4. 脑性耗盐综合征与脑肿瘤: Singh 等^[14]报道了 1 例 68 岁男性以中枢性甲状腺功能降低、肾上腺功能降低和性腺机能减退为主要表现的垂体瘤患者合并出现 CSWS,并指出热暴露、水分摄入不足可能加重 CSWS 的临床症状。Prochazka 等^[15]报道了 1 例 48 岁男性累及基底节区、右侧丘脑、压迫第三脑室的原发性中枢神经系统播散性大 B 细胞淋巴瘤患者,表现为 CSWS,患者在第 1 次化疗循环结束后,患者严重的低钠血症、低氯血症、低渗透压、明显的多尿症状逐渐缓解,证实淋巴瘤可能与 CSWS 有关,而化疗后随淋巴瘤细胞数目的减少患者 CSWS 症状得以逐渐缓解。脑肿瘤的部位为 CSWS 的致病灶定位提供了研究机会,但目前研究报道现状显示少量的病例报道限制了脑肿瘤与 CSWS 的相关性分析^[14, 15]。

5. 脑性耗盐综合征与自主神经功能紊乱: Abdel-Latif 等^[16]描述了 1 例 5 岁女性 Down 综合征患者因慢性寰枢椎半脱位和脱位骨折的齿状突导致急性脊髓损伤后出现 CSWS。朱烨等^[17]的研究报道显示,187 例急性颈髓损伤患者发生低钠血症的发生率为 89% (112/187),指出急性颈髓损伤的平面越高、损伤程度越重,则低钠血症程度越重,急性脊髓损伤后合并感染增加低钠血症的发生率,其导致低钠血症的病理机制可能与自主神经功能紊乱有关。Lenhard 等^[18]报道了 1 例以自主神经功能紊乱和中至重度低钠血症为主要临床表现的格林巴利综合征女性患者,指出该 GBS 患者出现低钠血症可能是自主神经功能紊乱临床表现之一。

6. 脑性耗盐综合征与脑膜脑炎: Roca 等^[19]发现 29 例成人结核性脑膜炎患者(其中 22 例为确诊为结核性脑膜炎患者,7 例为可能的结核性脑膜炎患者)低钠血症发生率为 52% (15/29),45% (13/29) 的患者出现低钠血症原因是 SIADH,并且指出,SIADH 和低胆固醇血症增加患者病死率,而 CWS 不是导致结核性脑膜炎患者出现低钠血症的常见原因。结核性脑膜炎导致的 CSWS 目前只见于病例报道^[20, 21]。In-

atomi 等^[22]首次报道了 1 例 8 岁男性无菌性良性脑膜炎患者并发 CSWS。Vega 等^[23]描述了 1 例 52 岁老年女性患者因李斯特菌性颅内感染引起脑炎、脑室周围炎及小脑和脑干脓肿,表现为低钠血症、低血压、尿钠增多、低尿酸血症、血肌酐及血尿素氮浓度降低而诊断为 CSWS 患者。Dass 等^[24]对 110 例侵袭性脑膜炎双球菌感染导致的脑膜炎患者进行了总结,发现导致患者低钠血症的主要并发症 SIADH 和 CSWS 发生率分别为 8.0% 和 0.9%。因此,结核性脑膜炎、无菌性脑膜炎、李斯特菌颅内感染、霉菌性脑膜炎等并发 CSWS 的发生率虽然比较低,但是当患者出现严重而持续的低钠血症、体液丢失、尿钠增多、低尿酸血症、血肌酐及血尿素氮浓度降低等临床表现时,笔者考虑到 CSWS 的可能,在治疗原发病的同时,需要补充丢失的氯化钠、水分及必要时口服氟氢可的松 [fludrocortisone, 10mg/(kg · d)] 等治疗^[25]。

三、小 结

低钠性脑病导致的脑组织改变可能与缺血缺氧性脑病存在相同的病理改变,如脑水肿、皮质层状坏死、基底节水肿及白质脱髓鞘、萎缩等,严重低钠血症(血钠浓度 < 115 mmol/L)住院患者临床症状主要为感觉功能改变 51.7%, 癫痫 22.5%, 恶心/呕吐 4.8%, 步态紊乱/频繁跌倒 3.6%, 构音障碍 2.2%, 昏迷状态 2.2%^[26]。结合 CWSW 的临床特点,有助于早期发现 CWSW 导致的低钠血症。补充 CSWS 导致的尿钠丢失量是治疗 CSWS 的关键。丁之明等^[27]通过对 9 例脑室腹腔分流术和脑室外引流术后化脓性脑室炎继发 CSWS 的患者研究,首次提出 CSWS 患者每日肾脏排钠量 = 患者 24h 尿钠量 = [治疗后预期应达到的血钠值 (mmol/L) - 治疗后实际血钠值 (mmol/L)] × 体重 (kg) × 0.6 (女性为 0.5) ÷ 17 + 每日生理需要量 (4.5g)。该公式为补充氯化钠提供了精确计算方案,成为临床治疗决策的重要参考指标,因为急性发作低钠血症的临床症状可能是爆发性的,而血钠浓度上升过快则会导致脑桥中央髓鞘溶解症^[7]。一般 CWSW 的治疗采用 3% 氯化钠高张盐水和 0.9% 的生理盐水,并更推荐于 0.9% 的生理盐水^[1, 7]。3% 的高张盐水补充速度为 1~2ml/(kg · h), 升高血钠浓度的速度为 1~2mmol/(L · h), 如果患者存在严重的症状,则需 4~5ml/(kg · h)。0.9% 的生理盐水有助于治疗脑性耗盐综合征,但能恶化 SIADH^[26]。并且,慢性低钠血症患者血钠波动大于 10mmol/(L · 24h) 有增加脑桥髓鞘溶解综合征的风险^[26]。

SIADH 是指中枢神经系统损伤后,刺激下丘脑,神经垂体轴兴奋,引起抗利尿激素(ADH / AVP)过度释放,水潴留,导致高血容量型稀释性低钠血症,较CSWS 为多见^[4]。CSWS 为一种较为少见的低血容量的低钠血症,主要特点为中心静脉压降低,负水平衡、尿排钠排钾、尿量增多,以及口渴、体重减少、直立性低血压、心动过速、黏膜干燥等低血容量性症状支持CSWS 的临床症状,补液试验有助于鉴别CSWS 和SI-ADH,其病理生理机制为补充等张盐水有引起血容量感受器饱和,通过减少抗利尿素分泌及促使肾脏排出过度的水分引起血钠浓度的恢复^[25]。

综上所述,导致脑性耗盐综合征的原因主要为蛛网膜下腔出血、脑手术后、脑外伤、脑肿瘤、自主神经功能紊乱、脑膜炎及脑炎,致病机制可能与房钠肽、脑钠肽分泌增多及交感神经功能紊乱导致肾脏过多排钠有关,临床特征为低血容量性低钠血症伴有多尿和尿钠增多,治疗原则为在治疗原发疾病时充分、规律性补充丢失的氯化钠和水分,氟氢可的松治疗有效,而更多的药物治疗尚在进一步研究中^[1]。

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