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大大分子高催乳素血症研究初报

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提 要 高催乳素血症可致卵巢功能紊乱，并导致不孕。然而，近年国外有若干报道少数本症伴存正常排卵周期与生育功能，引起人们注意。其循环中催乳素以生物活性较低的多聚型‘大’与‘大大’分子催乳素占主要成份，有人称作假高催乳素血症。通常使用胶层析方法检测到这类妇女循环中过量的多聚型‘大’与‘大大’分子催乳素成份。本文报告2例不孕妇女有高催乳素血症伴正常排卵周期。催乳素水平分别为133～165ng/ml和115～136ng/ml。胶层析结果显示其循环中‘大大’分子催乳素分别占83%及87%。例1同时合并有5.3×4.7mm垂体微腺瘤，经各项不孕原因检查，不孕并非高催乳素血症所致。

关键词 高催乳素血症 大大分子催乳素

高催乳素血症是不孕症的常见原因，在女性通常伴随无排卵月经，月经稀发，闭经等卵巢功能紊乱。然而近年来有若干报道高催乳素血症伴存正常卵巢功能，其循环中催乳素以较低活性的大大分子催乳素占主要成份，有人称作假高催乳素血症[1~5]。本文报告我院不孕症门诊所见2例高催乳素血症患者伴有正常的排卵周期，不孕原因并非高催乳素血症所致，其血清标本经胶过滤层析表明是以大大分子催乳素为主要成份的高催乳素血症。

病例报告

例1：韩某，女，37岁，结婚5年夫妇同居不孕。输卵管通液检查为通畅，丈夫精液分析正常，月经周期规则，28～30天，持续5～6天，基础体温测定均为典型双相曲线，激素测定：促卵泡成熟素(FSH)，黄体生成素(LH)，雌二醇(E_2)在正常范围，黄体期测定黄体酮(P)为15ng/ml，乳房检查挤压出乳液，曾用溴隐亭治疗1个月，溢乳有所减轻，但催乳素无下降，蝶鞍区CT检查显示5.3×4.7mm，垂体微腺瘤，血清样本经胶过滤层析2次均表明为大大分子催乳素为主的高催乳素血症。

例2：莫某，37岁，婚后同居10年不孕。丈夫精液分析异常。输卵管通液检查通畅，月经周期规则28～33天，持续5天，无经痛，基础温体呈双相型，乳房检查未挤出乳液。激素检查，黄体酮12 ng/ml，催乳素波动在115～136ng/ml，蝶鞍CT检查无异常。血清样本经胶层析诊断为大大分子催乳素所致高催乳素血症。

激素测定 全部测定的激素PRL、FSH LH、P、E_2等均采用天津利科(Lecco)生物科技有限公司供应的放射免疫测定药盒，各项质量控制符合要求。

层 析

1.方法 Sephacryl S-200(Pharmacia, Fine Chemical, Uppsala, Sweden)，经处理后用含0.25%牛血清白蛋白的0.5M磷酸钠缓冲液装于1.0×50cm层析柱上，每次层析用1 ml血清或血浆，含牛血清白蛋白的缓冲液以每小时6.0 ml过柱，用自动收集器(Fraction Collector LKB Bromma 2112 Heurac)收集每管1 ml，各管经放射免疫测定分析。层析前用Blue dextran (MW2000 000)、γ-Globulin (MW 160 000)及Albumin (MW 69 000) I-125 PRL过柱，收集各管，经过检测分析确定各收集管所在位置。

2.结果 2例经胶过滤层析结果：例1，血清总催乳素140ng/ml，大大分子催乳素占83%(116.2 ng/ml)，催乳素占17%(23.8 ng/ml)，无大分子催乳素。例2，血清总催乳素115 ng/ml，大大分子催乳素占87%(100 ng/ml)，而催乳素占13%(15 ng/ml)，亦无大分子催乳素。

讨　论

高催乳素血症所引起卵巢功能紊乱是众所周知的事实，然而大大分子催乳素为主的高催乳素血症未为人们所注意，后者是伴存正常排卵与生育功能，故有‘假高催乳素血症’之称。近年来通过胶过滤层析方法已经证明人类催乳素在血清中存在3种不同分子成分。正常妇女循环中分子量22 000 daltons的单型(monomeric form)催乳素占80～90%，是生物活性主要成分，多聚型(polymeric form)分子量5000及大于100 000 daltons的大与大大分子催乳素仅占催乳素的12～30%。多聚型催乳素真正性质还不十分清楚，但其与单型催乳素有类似的免疫活性，在剂量反应曲线中与抗体结合产生斜率是相似的，故可通过放射免疫检测[6]，多聚型催乳素仅有15%单型催乳素的受体活性[8]，这种低生物活性，常常用以解释大大分子催乳素为主体的高催乳素血症伴存正常卵巢功能，然而以循环中低生物活性的大大分子催乳素过量存在并不能充分地解释高催乳素血症伴存卵巢功能，因而 Anderson等[2]解释由于多聚型分子催乳素不易暴露其与受体结合点而妨碍了其与催乳素受体结合有关。Sweefoong [7]所观察认为大大分子催乳素妇女在生理时期，如月经周期、妊娠期、产后哺乳期，即使妊娠期总催乳素明显增加，而大大分子催乳素在循环中比例基本上没有改变。本文作者与 Fraser[8] 在悉尼已观察到使用 metoclopramide 或 TRH 刺激试验时，单型催乳素增加363%，而多聚性仅增17%，使用溴隐亭抑制试验，单型催乳素下降62%，多聚型仅下降21%。从临床所表明多聚型催乳素是低生物活性。实际意义上这类‘假高催乳素血症’是有别于‘真高催乳素血症’，因而必须小心诊断，特别是使用溴隐亭治疗高催乳素血症时必须警惕过度抑制具主要生物活性的单型催乳素，以免导致黄体功能不全的发生。

本文所报告在不孕门诊诊治的2例以大大分子催乳素为主的高催乳素血症，2例均有规律月经，从基础体温与黄体酮的测定提示是具有排卵周期，高催乳素血症并无影响其卵巢功能导致不孕。例1表现与文献报告不尽相同的是同时存在溢乳与垂体微腺瘤。从其血样本层析结果具有生物活性催乳素仅17%，23.8ng/ml(本室正常范围25ng/ml)，病者亦无分娩哺乳史，溢乳的解释可能与个体的乳腺受体敏感性升高有关[9]。垂体肿瘤特别是催乳素腺瘤与高催乳素血症关系密切，然而大大分子催乳素与垂体肿瘤的关系有人认为垂体肿瘤可以产生大分子催乳素，一般报告大分子催乳素的约占15～29%，而大大分子约占10%或更小[6,7]，Garnier 等[10]提到过1例催乳素水平为60ng/ml 的催乳素-生长激素分泌垂体肿瘤循环中大大分子催乳素占57.9%，大分子占13.4%（多聚型占71.8%），该例患肢端肥大症。例1是垂体肿瘤伴多聚型催乳素为主的高催乳素血症，并无肢端肥大症临床表现。然而本例确是一特殊病例，有待更一步深入检查研究。

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PRIMARY STUDY ON HYPERPROLACTINAMI A OF CIRCULATING IN BIG-BIG PROLACTIN

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Hyperprolactinamia may be associated with a variety of menstrual disorders and an important cause of female infertility. There have been several recent reports of women with apparently normal ovarian function who have by chance been found to have substantial hyperprolactinamia. In a high proportion of these women the prolactin was found by gel chromatography to be cifculating in polymeric forms (big-big prolactin and big prolactin). These polymeric forms have lower biological activity than the monomeric form of prolactin. This group of patients with might be called "false hyperprolactinamia". The present report describes two women with hyperprolactinamia, ovulatory cycles in our clinic. The levels of prolactin were varying from 133～165ng/ml in patient A, 115～136ng /ml in patient B and circulating forms of prolactin for woman A, B were big-big prolactin 83% and 87% respectively. Patient A has 5.3×4.7mm pituitary tumour by CT scanning. We found during the infertility workup some factors other than the reason for their infertility. As report of 2 cases it should contribute some imformations on biological activity and clinical significance of big-big prolactin and the relationship between polymeric form of prolactin and pituitary tumour was also discussed.

Key words Hyperprolactinamia Big-big prolactin