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【应用研究】

玻璃体内注射雷珠单抗治疗重度非增生型糖尿病视网膜病变伴黄斑水肿后患者脉络膜厚度的变化[△]

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Changes of choroidal thickness after ranibizumab treatment for non-proliferative diabetic retinopathy with macular edema

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【Key words】 non-proliferative diabetic retinopathy; macular edema; choroidal thickness

【Abstract】 Objective To observe the changes of choroidal thickness after ranibizumab treatment for non-proliferative diabetic retinopathy (NPDR) with macular edema, and determine the association between choroidal thickness and visual acuity.

Methods Twenty-three eyes from 23 patients diagnosed with NPDR and diabetic macular edema were treated with 3 monthly intravitreal injections of ranibizumab. The subfoveal choroidal thickness and central macular thickness were measured, and the best corrected visual acuity was recorded. Changes of subfoveal choroidal thickness, correlation between subfoveal choroidal thickness and best corrected visual acuity were assessed at 3 months follow-up. Results After 3 monthly anti-VEGF treatments, subfoveal choroidal thickness and central macular thickness decreased significantly, there was no statistical difference at 1 month and 2 months compared with pre-treatment (all $P > 0.05$), but there was statistical differences at 3 months compared with pre-treatment ($P = 0.04, 0.01$). In the treatment, the best corrected visual acuity increased gradually, there was no statistical difference at 1 month and 2 months compared with pre-treatment (all $P > 0.05$), but there was statistical differences at 3 months compared with pre-treatment ($P = 0.04$). Before the treatment, the subfoveal choroidal thickness was positive correlated with macular retinal thickness ($R^2 = 0.94, P = 0.00$); And the best corrected visual acuity before treatment and 3 months after treatment had a positive correlation ($R^2 = 0.93, P = 0.00; R^2 = 0.82, P = 0.00$). There was a positive correlation between central macular thickness and best corrected visual acuity at 3 months after treatment ($R^2 = 0.83, P = 0.00$). There was a positive correlation in the best corrected visual acuity between before treatment and 3 months after treatment ($R^2 = 0.84, P = 0.00$). Conclusion The subfoveal choroidal thickness is a clinical index to evaluate the efficacy of anti-VEGF in the treatment of diabetic macular edema. Baseline subfoveal choroidal thickness can be considered as one of the indicators of clinical efficacy in the short term.

【中图分类号】 R773.4

【关键词】 非增生型糖尿病视网膜病变;黄斑水肿;脉络膜厚度

【摘要】 目的 观察玻璃体内注射雷珠单抗治疗重度非增生型糖尿病视网膜病变伴黄斑水肿后患者脉络膜厚度的变化情况,明确脉络膜厚度与患者视力之间的相关性。方法 选取在我院确诊为重度非增生型糖尿病视网膜病变伴黄斑水肿患者23例(23眼),每月眼内注射1次雷珠单抗并连续接受3次治疗,记录患者治疗前以及治疗后1个月、2个月、3个月黄斑中心凹下脉络膜厚度,同时记录患者黄斑区视网膜神经上皮厚度和最佳矫正视力。分析黄斑中心凹下脉络膜厚度、黄斑区视网膜神经上皮厚度、最佳矫正视力的动态变化情况以及相关性的结果 玻璃体内注射雷珠单抗后1个月、2个月、3个月黄斑中心凹下脉络膜厚度和黄斑区视网膜神经上皮厚度均连续下降,前两个月与治疗前相比两指标差异均无统计学意义(均为 $P > 0.05$),第3个月时与治疗前相比,差异均有统计学意义($P = 0.04, 0.01$)。最佳矫正视力在治疗过程中持续得到改善,前两个月与治疗前相比差异均无统计学意义(均为 $P > 0.05$),第3个月时与治疗前相比,差异有统计学意义($P = 0.04$)。治疗前黄斑中心凹下脉络膜厚度与黄斑区视网膜神经上皮厚度之间存在正相关性($R^2 = 0.94, P = 0.00$);与治疗前和治疗后3个月最佳矫正视力之间均存在正相关性($R^2 = 0.93, P = 0.00; R^2 = 0.82, P = 0.00$)。治疗前黄斑区视网膜神经上皮厚度与治疗后3个月最佳矫正视力之间也存在正相关性($R^2 = 0.83, P = 0.00$)。治疗前最佳矫正视力与治疗后3个月最佳矫正视力之间同样存在正相关性($R^2 =$

0.84, $P=0.00$)。结论 黄斑中心凹下脉络膜厚度可以作为评价重度非增生型糖尿病视网膜病变伴黄斑水肿病情变化的有效临床指标,而且可以一定程度上预测抗血管内皮生长因子治疗的效果。

糖尿病黄斑水肿是糖尿病患者视力损害的主要原因之一^[1],视网膜血管结构的改变导致血-视网膜屏障破坏已经被证实在该病的发展过程中起关键作用,而脉络膜血管结构的变化可能也起到一定的促进作用。有学者推测脉络膜厚度变薄可能致使视网膜缺氧、血管内皮生长因子增加,进而破坏血-视网膜屏障导致糖尿病黄斑水肿^[2]。光学相干断层扫描的增强深度成像模式可以获得脉络膜的清晰图像并对脉络膜厚度进行定量分析^[3-11]。本研究旨在观察重度非增生型糖尿病视网膜病变伴黄斑水肿的患者接受雷珠单抗治疗后短期内黄斑中心凹下脉络膜厚度的变化情况。

1 资料与方法

1.1 一般资料 2015年6月至2016年7月于武汉爱尔眼科医院确诊为重度非增生型糖尿病视网膜病变伴黄斑水肿患者23例23眼入选本研究,其中男10例10眼,女13例13眼;年龄21~75(54.52±13.00)岁;所有受检者此前均未接受任何眼部相关治疗,均签署知情同意书。

1.2 黄斑中心凹下脉络膜厚度的测量方法 所有测量均由同一位经验丰富的医师独立完成,每眼测量3次,取其平均值。检查过程中,受试者均散瞳后使用光学相干断层扫描的增强深度成像模式扫描黄斑区,测量黄斑中心凹下脉络膜厚度,黄斑中心凹下脉络膜厚度定义为光学相干断层扫描影像中 Bruch

表1 治疗前后黄斑中心凹下脉络膜厚度、黄斑区视网膜神经上皮厚度以及最佳矫正视力的比较

指标	治疗前	治疗后1个月	治疗后2个月	治疗后3个月
黄斑中心凹下脉络膜厚度($l/\mu\text{m}$)	219.96±50.85	206.78±48.30	194.70±44.85	180.96±47.06
黄斑区视网膜神经上皮厚度($l/\mu\text{m}$)	474.39±95.63	426.13±87.08	407.04±89.07	383.17±88.33
最佳矫正视力	0.67±0.29	0.67±0.29	0.49±0.23	0.47±0.20

2.2 相关性分析 治疗前黄斑中心凹下脉络膜厚度与黄斑区视网膜神经上皮厚度之间存在正相关性($R^2=0.94, P=0.00$);与治疗前和治疗后3个月最佳矫正视力之间均存在正相关性($R^2=0.93, P=0.00; R^2=0.82, P=0.00$)。治疗前黄斑区视网膜神经上皮厚度与治疗后3个月最佳矫正视力之间也存在正相关性($R^2=0.83, P=0.00$)。治疗前最佳矫正视力与治疗后3个月之间同样存在正相关性($R^2=0.84, P=0.00$)。

3 讨论

虽然目前的研究尚无法完全阐明糖尿病黄斑水肿的发病机制,但血管内皮生长因子已被公认是参与糖尿病黄斑水肿病理生理过程的一个重要因子。当糖尿病黄斑水肿发生时,视网膜组织的缺氧以及高糖可引起血管内皮生长因子上调、视网膜血管通

膜高反射带至巩膜内表面高反射带的垂直距离。

1.3 玻璃体内注射雷珠单抗方法 睫状体平坦部进针将雷珠单抗注射液(瑞士 Novartis Pharma Schweiz,注册号 S20110085)0.5 mg(0.05 mL)注入玻璃体内。

1.4 观察指标 分别于治疗前及治疗后1个月、2个月、3个月测量所有患者的黄斑中心凹下脉络膜厚度、黄斑区视网膜神经上皮厚度并记录标准对数视力表的最佳矫正视力。

1.5 统计学处理 本研究所得数据使用 STATA 12.1 软件进行统计学分析。不同时间指标比较采用重复测量的方差分析, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 治疗前后黄斑中心凹下脉络膜厚度、黄斑区视网膜神经上皮厚度以及最佳矫正视力的变化 玻璃体内注射雷珠单抗后1个月、2个月、3个月黄斑中心凹下脉络膜厚度和黄斑区视网膜神经上皮厚度均连续下降,前两个月与治疗前相比两指标差异均无统计学意义(均为 $P>0.05$),治疗后3个月时与治疗前相比,差异均有统计学意义($P=0.04, 0.01$)。最佳矫正视力在治疗过程中持续得到改善,前两个月与治疗前相比差异均无统计学意义(均为 $P>0.05$),治疗后3个月时与治疗前相比,差异有统计学意义($P=0.04$,见表1)。

表1 治疗前后黄斑中心凹下脉络膜厚度、黄斑区视网膜神经上皮厚度以及最佳矫正视力的比较

指标	治疗前	治疗后1个月	治疗后2个月	治疗后3个月
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透性增高,导致视网膜血管的渗漏以及新生血管的产生等^[12]。做为人源化重组抗血管内皮生长因子抗体片段的雷珠单抗已被多项随机双盲多中心研究证实能有效改善糖尿病黄斑水肿并提高患者视力^[13]。但抗血管内皮生长因子治疗对脉络膜厚度变化的影响以及脉络膜厚度对糖尿病黄斑水肿的影响尚无充分的研究报道。

本研究观察到了重度非增生型糖尿病视网膜病变伴黄斑水肿患者在接受抗血管内皮生长因子雷珠单抗治疗后脉络膜厚度的变化情况,并且动态记录了短期内黄斑区脉络膜厚度变化的趋势。在本研究中,患者接受眼内注射雷珠单抗治疗后黄斑中心凹下脉络膜的总体变化趋势是厚度降低,但黄斑中心凹下脉络膜厚度在前两个月变化均不明显,直至第3个月,差异才具有统计学意义($P=0.04$)。而在随访过程中黄斑区视网膜神经上皮厚度和最佳矫正视

力的变化情况与黄斑中心凹下脉络膜厚度变化情况类似。我们分析以上结果可能是本研究样本量偏小而出现的抽样误差所导致的,也提示如果患者只接受1次或2次眼内注射药物治疗,那么患者眼部病情的变化较为细微。换言之对于重度非增生型糖尿病视网膜病变伴黄斑水肿的患者在接受雷珠单抗眼内注射治疗时完成每月1次连续3个月眼内注射的治疗方案对于维持疗效是非常必要的。

本研究对于黄斑中心凹下脉络膜厚度、黄斑区视网膜神经上皮厚度与最佳矫正视力间相关性分析显示:治疗后3个月最佳矫正视力与治疗前黄斑中心凹下脉络膜厚度、黄斑区视网膜神经上皮厚度和最佳矫正视力均存在正相关性,即在开始接受治疗前患者情况越好则治疗后越能保持较好的视力,这也进一步说明糖尿病视网膜病变患者早期治疗对于保存视功能的重要性。

脉络膜的主要功能是为外层视网膜提供血供和营养物质,这其中包括视网膜色素上皮层和光感受器层^[14]。以往研究发现糖尿病视网膜病变患者黄斑中心凹下脉络膜厚度低于正常人,而随着病情的发展黄斑中心凹下脉络膜厚度会进一步降低^[15-16]。糖尿病视网膜病变患者脉络膜厚度的变薄会引起脉络膜血流减少以及小动脉收缩变窄^[17-18],当脉络膜血供减少时,外层视网膜缺血,视网膜色素上皮细胞和微血管内皮细胞的血管内皮生长因子表达上调,进而破坏血-视网膜屏障最终造成黄斑水肿^[19-21]。由此可见,黄斑中心凹下脉络膜厚度可以作为评价重度非增生型糖尿病视网膜病变伴黄斑水肿病情变化的有效临床指标,而且可以一定程度上预测抗血管内皮生长因子药物治疗的效果。

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