Study of hypothalamic pituitary adrenal axis in patients of membranous nephropathy receiving modified Ponticelli regimen

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ABSTRACT

Pulse methyl prednisolone followed by oral prednisolone and abrupt switch to chlorambucil/cyclophosphamide (Ponticelli/modified Ponticelli regimen) is used in patients with idiopathic membranous nephropathy. This therapy where steroids are stopped abruptly is unphysiologic and expected to have hypothalamic pituitary adrenal (HPA) axis suppression; however, this has not been evaluated. A total of 13 consecutive adult patients with idiopathic membranous nephropathy who had completed modified Ponticelli regimen were studied. The regimen included administration of pulse methylprednisolone 1 g for 3 days followed by oral prednisolone 0.5 mg/kg/day for 27 days followed by oral cyclophosphamide at a dose of 2 mg/kg/day for the next month. This was repeated for three courses. Patients who had received corticosteroids prior to therapy were excluded. The HPA axis was evaluated after 1 month of completing the last course of steroid therapy. The evaluation was done using a low-dose adrenocorticotropic hormone stimulation test. A single intravenous bolus dose of synacthen (1 μg) was given at 9.00 am and the serum cortisol levels were estimated by radioimmunoassay at 0, 30, and 60 min. A peak cortisol level of 550 nmol/L or higher was considered as normal. Mean baseline cortisol levels was 662.3 ± 294.6 nmol/L and peak cortisol level was 767 ± 304.4 nmol/L. A total of 6 patients (46.2%) had low basal cortisol levels, only 3 (23%) had both basal and peak cortisol levels < 550 nmol/L suggestive of HPA axis suppression. To conclude, 23% of patients had suppression of HPA axis after modified Ponticelli regimen.

Key words: Adrenal insufficiency, adrenocorticotropic hormone stimulation, membranous glomerulonephritis, nephritic syndrome, pulse methyl prednisolone

Introduction

Over three decades ago, Ponticelli described an immunosuppressive regimen consisting of a combination of steroids and cytotoxic agents in the management of patients with idiopathic membranous nephropathy.[1] Ever since, this treatment has been in vogue and has been popularly known as the Ponticelli regimen. This therapy is of 6 months duration with corticosteroids being given on 1st, 3rd, and 5th month and chlorambucil in the 2nd, 4th, and 6th month, respectively.[1,2] In a prospective randomized controlled trial where in cyclophosphamide was used in place of cyclophosphamide (modified Ponticelli regimen) not only better remission, but also preservation of kidney function was observed.[3] Each steroid course is initiated with pulse methylprednisolone 1 g/day for 3 days followed by prednisolone 0.5 mg/kg/day for the remaining 27 days. At the end of the 1st, 3rd, and 5th months in which the patient receives steroids, there is an abrupt change over to chlorambucil or cyclophosphamide in Ponticelli and modified Ponticelli regimen respectively without any steroid tapering.[3]

A well-documented adverse effect of steroid treatment is suppression of the hypothalamic pituitary adrenal (HPA) axis.[4] Any patient who has received 20-30 mg/day of prednisone or more for more than 5 days is at risk for the above complication.[5] These patients are at risk of adrenal crisis when subjected to stress. A slow taper of corticosteroid therapy may facilitate recovery of HPA axis.

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Modified Ponticelli regimen has been the recommended standard of care in the management of patients with active immunogen (IMGN). However, the steroids are stopped abruptly without any tapering in the 1st, 3rd, and 5th month resulting in inability of the adrenal gland to return to their normal physiological secretion. However, there are no data available to justify the above statement and this study was undertaken to evaluate HPA in patients of IMGN.

Materials and Methods

Thirteen consecutive adult patients with idiopathic membranous nephropathy (age >18 years) who were complaint and successfully completed modified Ponticelli regimen were included in the study. The regimen included administration of intravenous (IV) pulse methylprednisolone 1 g over 1 h for three consecutive days followed by oral prednisolone 0.5 mg/kg/day for 27 days. This was followed by oral cyclophosphamide at a dose of 2 mg/kg/day for the next month. The whole cycle was repeated for a total of three courses.[3] Patients who had received corticosteroids prior to starting Ponticelli regimen or any clinical history suggestive of prior adrenal disease and the HPA suppression, prior comorbidities (diabetes mellitus and asthma) and patients who received hepatic cytochrome inducer/inhibitor or any other drugs, which could affect the steroid levels or HPA axis were excluded from the study.

Protocol

The HPA axis was evaluated after 1 month of completing the last course of steroid therapy. The evaluation was done using a low dose (1 μg) adrenocorticotropic hormone (ACTH) stimulation test.[6,7] Informed consent was taken, and the patients were given a single bolus dose of synacthen (1 μg) IV at 9.00 am after collecting the basal samples (0 min) (1 mcg was used instead of 250 mcg, as the latter dose would be too high in patients with prior normal functioning adrenals). Further samples were drawn at 30 and 60 min after ACTH dose for cortisol measurement.

Assay

Serum total cortisol was performed using radioimmunoassay (Beckman Coulter). Results were obtained from the standard curve by interpolation. The lowest detection limit of the assay was 5 nmol/L. The intra- and inter-assay coefficient of variation being <8%. A peak cortisol level of >550 nmol/L or higher was considered as a normal response to the test.

Results

A total of 13 patients (8 males and 5 females) were included in the study. Mean age was 34 ± 6.7 years. The results of the ACTH stimulation test of the 13 patients are as in Table 1. Mean baseline cortisol level was 662.3 ± 294.6 (300-1100) nmol/L and mean peak cortisol level was 767 ± 304.4 (330-1200) nmol/L. A total of 6 patients (46.2%) had low basal cortisol levels (<550 nmol/L). However, only 3 (23%) had both basal and peak cortisol levels <550 nmol/L suggestive of HPA axis suppression. None of the patients had symptomatic adrenal insufficiency. No untoward incident was observed in patients undergoing the test.

Discussion

Alternating cycles of steroids and cytotoxic agents are the recommended as the first-line agent for the management of idiopathic membranous glomerulonephritis. At present, this is the only therapy to have long-term preservation of renal function in patients with idiopathic membranous glomerulonephritis.[3] The true prevalence of HPA axis suppression following a course of corticosteroid therapy is not known. This is probably because high-dose glucocorticoids are seldom abruptly stopped. Gradual steroid dosage taper may allow recovery of HPA axis. Most physicians have developed their own individual schedules in tapering steroids. No prospective studies have defined optimal methods of dosage reduction. Since the symptoms and signs of adrenal insufficiency are nonspecific, confirming the diagnosis requires documentation of subnormal cortisol levels that remain inappropriately low despite provocation.[8]

Traditional testing of HPA axis function has relied essentially upon insulin induced hypoglycemia or metyrapone challenge.[8,9] However, both of these tests are uncomfortable for patients and can also have serious adverse effects. The short ACTH test using 250 μg of ACTH has been validated by several studies as a good

Table 1: Results of the low dose synacthen test (cortisol levels in nmol/L)

Patient number	Baseline (0 min)	30 min	60 min	Peak
1	440	380	410	440
2	370	280	260	370
3	300	310	330	330
4	1000	800	520	1000
5	440	780	560	780
6	1100	1200	1200	1200
7	340	680	680	680
8	660	560	560	560
9	800	920	600	920
10	1060	1040	860	1040
11	540	860	500	860
12	1000	1200	1200	1200
13	560	920	920	920
All cases	662.3±294.6	763.8±309.8	661.5±301.5	775.3±309.7

measure of HPA axis function.[10,11] It does not have the side-effect profile of the previous tests. However, the dose of ACTH used may produce supraphysiologic plasma levels and may result in a normal plasma cortisol level in patients with partial adrenocortical insufficiency. The low dose (1 μg) ACTH test overcomes this problem and has been proved to be more sensitive than the conventional ACTH test.[12,13] The same was used in this study. Estimation of free cortisol would be more appropriate than total cortisol in patients of nephrotic syndrome due to loss of cortisol binding globulin (CBG) in urine. However, due to lack of facility for estimation of free cortisol/CBG, only total cortisol levels were estimated.

It is surprising that despite the unusual regime of steroids used by Ponticelli, there have been no studies until date of its effect on the HPA axis. However, in idiopathic nephrotic syndrome in children, Moel *et al*. have reported a low prevalence of HPA axis suppression.[14] Nine of the 10 frequent relapsers had a normal ACTH stimulation test, whereas all infrequent relapsers had normal responses. Twenty percent of our patients had evidence of HPA axis suppression. This significantly higher prevalence could be because of the sudden cessation of steroids in the Ponticelli regimen. It would have been ideal to have a comparison cohort of IMGN, where in steroids are not given but it would be difficult to find a comparative group, as the alternative therapy for membranous glomerulonephritis is calcineurin inhibitors (cyclosporine or tacrolimus) along with low dose steroids.

The exact glucocorticoid dose or duration of therapy that leads to HPA axis suppression is not well-defined. In another study of 184 children with steroid sensitive nephrotic syndrome treated with varying duration of steroids (2-6 months), HPA axis was studied in 67 by the synacthen test.[15] There was no significant correlation between suppression of adrenocortical function and treatment duration. A similar result is reflected in our study. Although all the patients received almost the same cumulative dose and duration of therapy, only 3/13 patients showed HPA axis suppression. We suspect that must be additional factors other than abrupt cessation that determine if a patient is destined to develop HPA axis suppression. Patients whose HPA axis is suppressed may require a prolonged period for recovery, which may extend even up to 1-year. Hence, they may need to take glucocorticoid supplements at times of illness or injury until the axis recovers. HPA axis needs to be tested in the patients of idiopathic membranous nephropathy on Ponticelli/modified Ponticelli regimen.

Nearly half our patients had basal cortisol levels <550 nmol/L, of which only 23% had <550 nmol/L after ACTH administration suggesting an intact axis in the majority. Thus low basal levels of cortisol do not necessarily predict HPA axis suppression and a stimulation test need to be performed to detect these cases. None of our patients had symptomatic HPA axis suppression. Doi *et al*.[16] have suggested a cut-off value of 600 nmol/L after ACTH stimulation as diagnostic of HPA axis suppression, while values between 400 and 600 nmol/L are in gray area. If we take 600 nmol/L as the cut-off limit then 4 in place of 3 would have adrenal insufficiency. We have taken a cut-off of 550 nmol/L based on our experience at this center.[7] In this study, HPA axis was studied 1 month after completion of the regimen, which could have given some time for HPA axis to recover. HPA axis suppression could have been higher if it was tested immediately after the completion of 1st cycle.

Conclusion

This study shows a 23% prevalence of asymptomatic HPA axis suppression after completion of the modified Ponticelli regimen for treatment of idiopathic membranous nephropathy, after a sudden cessation of steroid therapy. HPA axis needs to be tested in these patients. This side-effect of corticosteroid therapy can be detected only by an appropriate provocative test.

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