Case Report

ACTH-induced improvement in the nephrotic syndrome in patients with a variety of diagnoses

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Introduction

In the fifties and the sixties, ACTH was widely used for the treatment of childhood nephrosis probably caused by minimal change disease in most cases [1,2]. This treatment was provided in lieu of steroids since it does not suppress the adrenal glands and there were hopes of less growth stunting. There are a few reported cases of ACTH treatment in nephrotic patients who had not been biopsied but probably suffered from other diseases than minimal change disease [3,4]. These patients received huge doses of short-acting ACTH for days or weeks and some of them seemed to respond, at least partially. During the last few decades the use of ACTH has been limited due to the fact that the preparation must be given parenterally.

We have reported that treatment with a synthetic ACTH analogue (ACTH1–24; Synacthen Depot) was associated with reduced albuminuria in patients with idiopathic membranous nephropathy [5]. This was incidentally noted during a treatment trial in nephrotic patients with idiopathic membranous nephropathy which focused on the lipid-lowering effects of ACTH [5]. The marked reduction in albuminuria observed in all the study participants suggested that this effect was not coincidental.

During the time interval between the above study and an ongoing controlled trial, we continued to administer ACTH to nephrotic patients who were not expected to respond to steroids. Roughly half of the patients suffered from idiopathic membranous nephropathy but the rest had different diagnoses. We now report these cases.

Cases

All 23 nephrotic patients submitted to us for ACTH treatment during the period in question are included in the report (Table 1). Eleven patients had recently been treated with steroids without response. Regarding the rest of the patients, there was a reluctance to expose them to immunosuppressive agents due to different clinical conditions and the same applied to steroids since they were not expected to be effective. There were 14 females and nine males. The median age was 59 (20–84) years. There were 10 patients with idiopathic membranous nephropathy, six patients with mesangio-proliferative glomerulonephritis, two patients with minimal change disease, two patients with diabetes nephropathy, one patient with focal segmental glomerulosclerosis, one patient with mesangiocapillary glomerulonephritis type 1, and one patient with hereditary nephropathy.

ACTH was given in the form of Synacthen Depot 1 mg/ml (ACTH1–24) i.m. or s.c., which was administered at individual doses depending on body weight and side effects [0.5 mg once a week, 1 mg once a week, 0.75 mg twice a week or 1 mg twice a week (the median maximal dose was 25.0 (8.3–30.0) μg/kg/week)]. The doses were tapered at the end of treatment. The duration of treatment differed depending on the rate of response and possible side effects (Table 1). All the patients were on a statin and an ACE inhibitor or an angiotensin II receptor blocker at the start of ACTH treatment. Such treatment was generally stopped when the patient was well into remission. Most of the patients were on a diuretic at the start of ACTH treatment but this was stopped at the time of remission. Antihypertensive treatment was in no case increased during ACTH treatment.

Biopsy-proven diagnosis, previous immunosuppressive treatment, duration of ACTH treatment and follow-up time for each patient are given in Table 1. The individual urinary albumin excretion before and after ACTH treatment as well as at the end of the follow-up period is also given in Table 1. The median
serum albumin concentration was 19 (10–23) g/l before treatment, 35 (17–43) g/l after treatment and 34 (22–49) g/l at the end of the follow-up period. At the same time points, the median serum creatinine concentrations were 103 (64–481) μmol/l, 89 (45–326) μmol/l and 94 (45–1000) μmol/l, respectively. With one exception (no. 19), the patients responded to ACTH. Patient no. 19 had a fulminant course and was on dialysis within 6 months of diagnosis. There was indeed a decrease in albuminuria during ACTH treatment in this case but this was associated with reduced renal function. Otherwise, the least convincing responses were observed in the patients who suffered from focal segmental glomerulosclerosis (no. 13) and hereditary nephropathy (no. 23) (50 and 75% reductions in albuminuria, respectively). Four patients had relapses of their disease during the follow-up time (nos 10, 11, 20 and 23). Two of these patients were treated with and responded again to ACTH (nos 10 and 20). Patient no. 11 was maniodepressive and, therefore, the ACTH treatment was not repeated. The relapse experienced by patient no. 23 was associated with pregnancy.

Discussion

We present 23 nephrotic patients who were treated with a slow-release preparation of ACTH at the maximal dose of 1 mg twice a week for 2–11 months. The patients suffered from non-proliferative glomerulonephritides, proliferative glomerulonephritides, diabetes nephropathy or hereditary nephropathy. Four patients had a relapse during the follow-up time, all four with different histopathological diagnoses.

In a previous report, we accounted for five patients with idiopathic membranous nephropathy who received long-term treatment with ACTH [5]. Now 10 additional patients with this diagnosis have been treated with ACTH. Nine of these showed an adequate response and did not relapse during the follow-up period. Patient no. 10 initially responded well to ACTH but soon had a relapse after treatment was stopped and then, again, responded to ACTH. Even though this is not a controlled study but a case series the conclusion can be drawn that ACTH is a promising treatment for the nephrotic syndrome associated with idiopathic membranous nephropathy. As yet, no consensus has been reached about the therapy of this disease even though treatment with alkylating agents [6,7] as well as cyclosporine [8] has been reported and, therefore, the search for new treatment forms seems to be warranted.

In the present report, it was not only patients with idiopathic membranous nephropathy who responded to treatment with ACTH but also patients who were nephrotic due to other diseases such as proliferative glomerulonephritides, diabetes nephropathy and...
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hereditary nephropathy. Thus, ACTH seems to exert a non-specific antiproteinuric effect rather than a specific effect against idiopathic membranous nephropathy.

The mechanism behind the antiproteinuric effect of ACTH has not been elucidated. Since the observations are uncontrolled it is possible that we are dealing with spontaneous remissions of the nephrotic syndrome. However, the similar timing of the reduction in proteinuria in all cases in combination with an effect even in patients with diabetes nephropathy argues against spontaneous remissions. The increase in steroid load induced by ACTH treatment might play a role. An antiproteinuric effect of steroids has only been shown convincingly in certain diseases such as minimal change disease but it is possible that the large pulse dose of endogenous steroids induced by ACTH acts differently from the conventional peroral steroid treatment. The lipid-lowering effect of ACTH, observed in this as well as in other patient materials [5,9–11], possibly influences the proteinuric disease. There is a large body of evidence linking hyperlipidaemia with the progression of proteinuric renal disease [12] and lipid-lowering treatment has been reported to induce a reduction of urinary protein excretion [13] in some studies but not all [14]. However, lipid-lowering treatment has not previously been associated with such a dramatic reduction of proteinuria as observed in the present cases. The simultaneous treatment with ACE-inhibitors and statins may have interacted with ACTH in a favourable fashion. Conceivably, many of the above-mentioned factors interact but it is also possible that ACTH exerts some specific beneficial effect on the renal haemodynamics or the stability of the glomerular basement membrane.

For the time being, the ACE inhibitors and angiotensin II receptor blockers are the only substances that are in clinical use as non-specific antiproteinuric agents [15]. Their effect is generally less than the presently reported effect of ACTH and it is often accompanied by a reduction of the glomerular filtration rate. The improvement in the glomerular filtration rate observed in many of the ACTH-treated patients may be secondary to increased renal blood flow, caused by the remission of the nephrotic syndrome, or this may be a separate phenomenon.

ACTH can obviously be used when steroid treatment is indicated. Moreover, ACTH seems to influence the nephrotic syndrome in patients with different diagnoses even though this case series does not identify the patients that benefit more from ACTH than other therapy. More information is needed before any general recommendations can be given.

Conflict of interest statement. None declared.

References


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