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Adrenocorticotropic hormone: Therapeutic use and effects in nephrotic syndrome

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Abstract

Background: NS is defined by the presence of significant proteinuria, which leads to low levels of albumin in the blood and the development of edema. This occurs as a result of damage to the glomerular filtration barrier. Corticosteroids are the main therapeutic approach for NS. Prolonged usage of steroids can result in numerous side effects, including steroid resistant NS, which poses a difficult challenge for treatment and can cause substantial morbidity and mortality. Although efforts have been made to decrease the use of steroids by employing non-steroidal immunosuppressive drugs for rapid recovery, these treatments have also exhibited adverse consequences. These difficulties have prompted the notion of utilizing ACTH in these situations.

Objective: This study seeks to analyze the efficacy of ACTH by thoroughly examining its mechanism and comparing it to conventional treatment for NS.

Summary and important messages: The study demonstrates that ACTH has the potential to not only decrease protein loss but also reduce the occurrence of relapses and the amount of glucosteroids required. This suggests that ACTH could be a viable treatment alternative. The exact mechanism is currently unidentified, while the MCR1 agonism linked to ACTH suggest a renoprotective mechanism that is beneficial in NS. A comprehensive analysis using a large-scale randomized controlled trial is necessary to fully comprehend the effectiveness and safety profile of ACTH in improving the quality of care for patients.

Keywords: ACTH; Nephrotic syndrome; Nephrology; Proteinuria; Glucocorticosteroids

1. Introduction

Nephrotic syndrome (NS) is defined by the presence of proteinuria of more than 3.5 g per day in adults or more than 50 mg/kg/day in children, and hypoalbuminemia [1]. Other common but non-defining features are edema and hyperlipidemia. The incidence of nephrotic syndrome in adults is 3 cases per 100,000 per year [2]. It can be due to primary and secondary causes. Primary or idiopathic causes include minimal change disease [MCD], focal segmental glomerulosclerosis [FSGS], membranous nephropathy [MN]. Secondary causes for nephrotic syndrome include infections, diabetic mellitus [DM], systemic lupus erythromatosus [SLE], drug reactions, malignancies etc.

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The associated complications of NS can cause significant morbidity to affected population, those include infections, metabolic derangement like hypocalcemia with subsequent bone abnormalities, thromboembolism, hyperlipidemia, and related atherosclerosis. Most of these complications are thought to happen due to loss of physiologically important proteins in urine or subsequent compensatory protein synthesis by the liver [3].

Various pharmacological treatments have been utilized based on the cause of NS. Corticosteroids have been a key component in many of these treatment plans. However, even in patients with steroid-sensitive nephrotic syndrome (SSNS), a significant subgroup experiences a frequently-relapsing nephrotic syndrome (FRNS). FRNS is defined as having 2 or more relapses within a 6-month period or 4 or more relapses within one year. In some cases, these patients may also develop steroid-dependent nephrotic syndrome, characterized by two or more consecutive relapses of nephrotic syndrome while on corticosteroid therapy or within 14 days of stopping therapy [4].

Adrenocorticotropic hormone (ACTH) is a significant peptide hormone that is secreted by the pituitary gland. It has a crucial role in both the endocrine and neuroimmune systems. The FDA approved the purified form of H.P. Acthar Gel in 1952 for the purpose of reducing proteinuria and hyperlipidemia in pediatric nephrotic syndrome. It was replaced by oral corticosteroids because of its high cost and inconvenient administration [5]. The failure of a significant subset of NS patients to respond steroids prompted the search for alternative treatments, including reexamination of ACTH.

This study aims to review current understanding of effectiveness of ACTH in NS of various etiologies by analyzing the efficacy and safety of ACTH with the current standard therapies.

2. Pathophysiology of Nephrotic Syndrome

NS arises from the disruption of the glomerular filtration barrier, resulting in the presence of proteinuria (more than 3.5 grams/day in adults and more than 50mg/kg/day in children) and low levels of albumin in the blood. The filtration barrier is composed of three layers: fenestrated endothelial cells, a basement membrane, and podocytes. Podocytes are specialized cells responsible for providing support and ensuring the proper functioning of the kidney's filtration system. Podocytes has a restricted capacity for regeneration. Genetic mutations or injury to podocytes can lead to changes in podocyte function. Podocytes also participate in the production of glomerular basement membrane (GBM) and the formation of fenestrations in endothelial cells. Therefore, damage to the podocytes also impacts the nearby structures, modifies the permeability of the glomerulus, and results in proteinuria [6,7,8].

Proteinuria results in substantial depletion of albumin, which serves as the principal controller of plasma colloid osmotic pressure. The reduction in plasma osmotic pressure results in the accumulation of fluid in the interstitial spaces, causing edema. The depletion of protein also results in increased salt retention, thereby causing an upregulation of a proprotein convertase called PCSK9 [9]. This has been associated with an elevation in the production of cholesterol by the liver, resulting in hyperlipidaemia [10]. The pathophysiology of NS is shown in Figure 1.

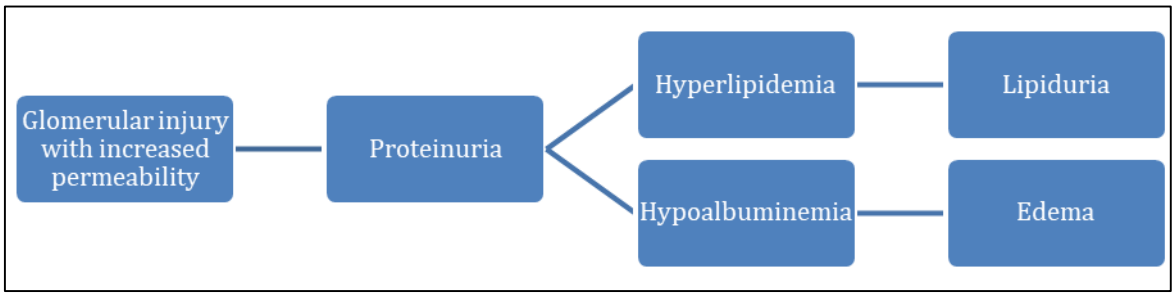

Figure 1 Pathophysiology of Nephrotic syndrome

3. Adrenocorticotropic Hormone: Mechanism and General Uses

ACTH is a tropic hormone produced by the anterior pituitary and controlled by hypothalamic-pituitary axis (HPA). ACTH regulates cortisol and androgen production. Pro-opiomelanocortin (POMC) gives rise to ACTH and melanocyte-stimulating hormone (MSH) [11].

ACTH was extracted from pig and sheep pituitary gland by isoelectric precipitation in the 1940s. One preparation of ACTH was commercially available as sterile powder reconstituted with isotonic saline for intramuscular injection. In

the early 1950s, intramuscular injections of Cortisone and ACTH were first being used for treatment for nephrotic syndrome in children by Arneil and Wilson from Glasgow. these were relatively short courses, 5days of daily 100–300mg of intramuscular (IM) cortisone in the first study and 40–80mg of an ACTH IM injection for 12days in the second study H. P. Acthar® Gel, a form of ACTH therapy, is a highly purified form of ACTH and is delivered as a gel to provide extended release of ACTH following injection. It was initially FDA-approved in 1952 for the reduction of proteinuria and hyperlipidemia associated with pediatric NS. However, given its high cost and subcutaneous administration, it was replaced by synthetic oral glucocorticoids, a cheaper and more convenient treatment. Thus, steroids have become the first line of treatment [12]

Corticotropin releasing hormone (CRH) is released from the hypothalamus. CRH stimulates the anterior pituitary to release ACTH. ACTH acts on the adrenal cortex to release cortisol and androgens. The increase in cortisol provides a negative feedback system to decrease the amount of CRH released from the hypothalamus and activation of protein kinase A. ACTH works on G protein-coupled receptors on extracellular membranes on zona fasciculata and zona reticularis of the adrenal cortex. cAMP is the secondary messenger system. Activation of the g-couple receptor activates adenylyl cyclase, thus increase cAMP production. ACTH plays a role in glucose metabolism and immune function. The circadian rhythm influences cortisol secretion [13]. The highest levels of cortisol are seen in the early morning, and the lowest levels are in the evening. This concept is important for diagnostic testing. The use of ACTH and its mode of action in different disorders is shown in Table 1.

Table 1 The use of ACTH and its mode of action in different disorders

Disorder	Use of ACTH	Mode of Action
Infantile Spasms (West Syndrome)	First-line treatment	Stimulates adrenal cortex to produce corticosteroids, reducing CNS excitability.
Multiple Sclerosis (Acute Relapse)	Management of acute exacerbations	Increases endogenous corticosteroid levels, reducing inflammation and autoimmune activity.
Adrenal Insufficiency (Secondary)	Diagnostic and therapeutic	Stimulates adrenal glands to produce cortisol, assessing adrenal reserve and function.
Congenital Adrenal Hyperplasia	Adrenal function testing	Assesses adrenal gland responsiveness to ACTH, guiding steroid replacement therapy.
Rheumatoid Arthritis	Short-term management during flares	Enhances corticosteroid production, reducing joint inflammation and immune response.

Treatment of relapsing NS is challenging despite the advent of newer immunosuppressive medications. The extensive side-effect profile of glucocorticoids limits their use for prolonged therapy. Alternative medications such as animal derived ACTH have been recently used in pediatric and adult patients to treat resistant diseases MCD, FSGS, membranoproliferative glomerulonephritis (MPGN) etc. ACTH has shown to induce NS remission not amenable to steroids and other immunosuppression medications. A multicenter small randomized controlled trial (RCT) in patients with idiopathic MN demonstrated superior outcomes with ACTH when compared with the standard Ponticelli regimen [15]. It is hypothesized that the anti-proteinuric action of ACTH is not solely attributed to its steroidogenic effects, because several case series showed patients with steroid-resistant NS responded well to ACTH therapy [14]. Increasing evidence suggests that ACTH may exert a glomerular protective and antiproteinuric effect via multipronged mechanisms, including direct podocyte protection, lipid lowering action and potent melanocortinergic activities [15].

4. Results

NS is characterized by proteinuria, hypoalbuminemia, and edema due to damage of glomerular filtration barrier. The analysis of effectiveness of ACTH and multiple RCT have proved that ACTH can play a renoprotective role in the different etiologies of NS and in their complications. The studies have shown ACTH is effective in steroid resistant glomerular diseases, independent of its steroidogenic activities. The activity of ACTH on melanocortin receptors MC1R and MC5R expressed by glomerular podocytes contribute to its antiproteinuric effects. In a retrospective study done at Zhejiang University School of Medicine that included 38 children with frequently relapsing and steroid-dependent nephrotic syndrome, ACTH was shown to improve cumulative sustained remission rate, lower relapses rate and decrement in the dosage of glucocorticoids. Addition of ACTH to the conventional therapy also seems to be promising in patients with FRNS, SDNS and SRNS. The number of studies on this hypothesis is limited and thus, warrants large scale RCT analysis.

5. Discussion

ACTH is a pituitary polypeptide hormone that plays a major role in the hypothalamic-pituitary-adrenal axis. The use of ACTH in the treatment of nephrotic syndrome in both adults and children has been explored many times over the years. Steroids have been the mainstay of treatment of NS but steroid resistance is common and is an important risk factor for the development of CKD [16]. Approximately 50% of children have been shown to progress to frequently relapsing NS or steroid dependent NS [17].

Many studies have shown that ACTH improves outcomes in NS. ACTH has shown reduction in proteinuria by binding to the melanocortin 1 and 5 receptors on the podocytes [18]. In a retrospective study done at Zhejiang University School of Medicine that included 38 children with frequently relapsing and steroid-dependent NS, ACTH has improved cumulative sustained remission rate, lower relapses rate and decrease the dosage of glucocorticoids [19].

In other RCT, ACTH has also been shown to be effective in steroid resistant glomerular diseases which indicates that ACTH has a potential role in treating these diseases independent of its steroidogenic activities [20]. Addition of ACTH to the conventional therapy also seems to be promising in patients with FRNS, SDNS and SRNS [21]. The number of studies on this hypothesis is limited and thus, warrants more extensive research.

ACTH has a similar side effect profile to glucocorticoids. These include increased appetite, behavioral changes and cushingoid symptoms [22]. The effects of ACTH in NS is shown in Figure 2.

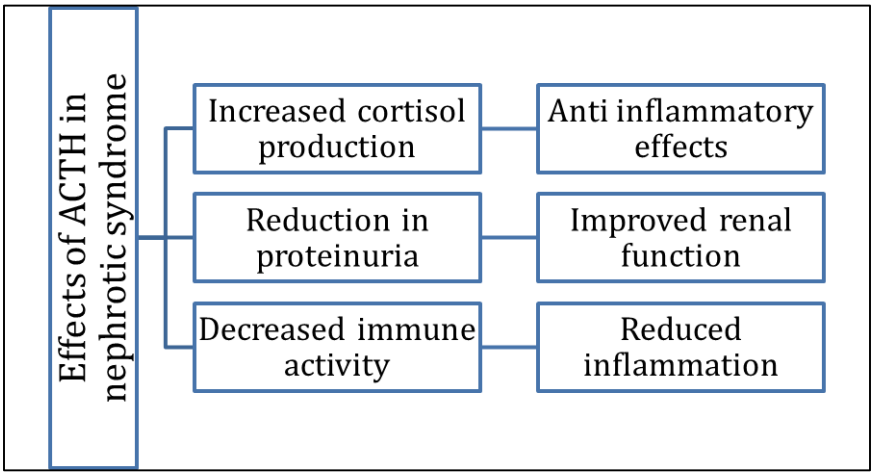

Figure 2 Effects of ACTH in NS

6. Conclusion

NS, presented with proteinuria and hypoalbuminemia can become challenging as glucocorticoids not only give side effects but can turn NS into steroid resistant. There is renewed interest in use of ACTH as a treatment option of NS and it represent a novel therapeutic strategy in proteinuric nephropathies such as FRNS and SDNS. Although the exact mechanism of action of ACTH is yet to be clarified, various proposed explanations include MCR1 receptor agonist action on podocytes along with systemic immunomodulation and anti-inflammation that has shown efficacy in reducing proteinuria and renoprotective effects.

The use of ACTH either as an alternative or adjunctive to conventional treatment modalities including drugs like immunosuppressive and glucocorticoids for NS regardless of underlying diagnosis may provide promising outcomes in terms of less relapses and long-term steroid induced side effects which directly influences the quality of patient care. Although the clinical findings are encouraging, most of them are derived from observational studies, thus large-scale RCT are required to determine its efficacy and safety in larger population. If validated through more research ACTH can be incorporated into clinical practice as a recommended treatment option for NS and can be considerable for personalized patient care.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Author Contributions

- Gul-E-Zernab : Substantial contributions to the conception or design of the work;
- Nitesh, Shivkumar: the acquisition, analysis, or interpretation of data for the work;
- Raef, Sri, Manal: Drafting the work or reviewing it critically for important intellectual content;
- Dr. Srijamya, Dr. Munawar: Final approval of the version to be published; AND Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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