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Research Article

Managing Frequently Relapsing Childhood Nephrotic Syndrome: A Novel Combination of Synacthen and Mycophenolate Mofetil

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Abstract

Childhood nephrotic syndrome is a prevalent renal disorder characterized by generalized edema due to hypoalbuminemia from heavy proteinuria. This syndrome can be classified as primary or secondary, with the majority of cases being primary. Historical perspectives on nephrotic syndrome illustrate significant advancements in understanding its pathology and treatment, beginning with early descriptions in the 15th century and evolving through the introduction of terms like "nephrosis."

Current management primarily relies on corticosteroids, but issues such as frequent relapses and steroid dependency necessitate alternative therapies. Recent approaches include the use of levamisole and mycophenolate mofetil, alongside the resurgence of intramuscular ACTH (synacthen) as a treatment option.

This article presents a case study of a boy with frequently relapsing steroid-dependent nephrotic syndrome, successfully treated with a novel combination of intramuscular synacthen and mycophenolate mofetil.

This regimen effectively reduced the required dosage of steroids while minimizing associated adverse effects, particularly psychiatric symptoms. The findings underscore the potential for innovative therapeutic strategies in managing challenging cases of childhood nephrotic syndrome.

Keywords: frequently relapsing nephrotic syndrome; challenging cases; innovative therapeutic strategies

Introduction

Childhood nephrotic syndrome is primarily characterized by generalized edema due to hypoalbuminemia from significant proteinuria. Most cases are primary, with historical descriptions dating back to the 15th century. Key advancements in understanding and treating the syndrome include the introduction of terms like "nephrosis" by Friedrich von Müller and the distinction between inflammatory and non-inflammatory renal diseases by Franz Volhard and Theodor Fahr [1-18].

In 1484, Cornelus Roelans from Belgium likely described one of the first cases of nephrotic syndrome, noting whole-body swelling in a child [1]. In 1722, Theodore Zwinger from Basel provided a detailed account of childhood nephrotic syndrome, highlighting reduced urine output and attributing this to obstruction of the renal tubules [2].

In 1827, Richard Bright (Figure 1A) suggested that generalized edema combined with proteinuria is indicative of renal disease [3].

Figure-1A: Richard Bright (September 28, 1789-December 16, 1858) was an English physician

John Bostock (Figure 1B) observed a correlation between high urinary protein excretion and low serum protein levels [4].

Figure-1B: John Bostock, Jr. (June 29, 1773-August 6, 1846), an English physician and scientist

In 1846, George Johnson (Figure 1C) posited that the renal disease identified by Bright was a localized manifestation of a broader constitutional disorder. He also noted that not all cases of Richard Bright included albuminuria, which represents what Rayer called "Albuminous nephritis", hinting at the heterogeneous nature of Bright's disease [5].

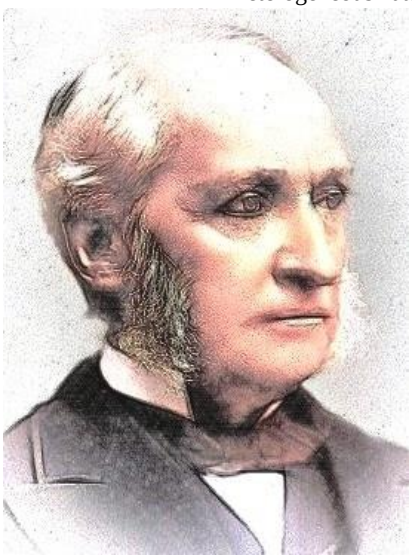

Figure-1C: George Johnson (November, 29 1818-June, 3 1896) was an English physician

In 1905, Friedrich von Müller (Figure 1D) introduced the term "nephrosis" to describe the histological changes in renal tubules which were thought to be degenerative, distinguishing these non-inflammatory disorders from "parenchymatous nephritis" which suggests an exudative and inflammatory disorder. Later, nephrosis has been used to describe the clinical condition which has been increasingly known nephrotic syndrome [6].

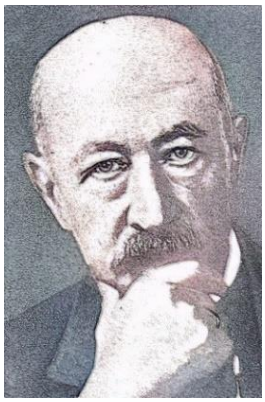

Figure-1D: Friedrich von Müller (September 17, 1858-November 18. 1941), a German physician

In 1914, Franz Volhard (Figure 1E) and Theodor Fahr (Figure 1F) reaffirmed the distinction between nephroses, a non-inflammatory disease and inflammatory nephritides in their classification of renal disorders [7].

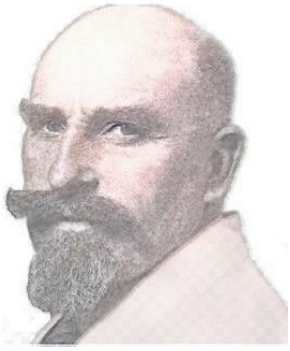

Figure-1E: Franz Volhard (May 2, 1872-May 24, 1950), a German physician

Figure-1F: Karl Theodor Fahr (October 3, 1877-October 29, 1945), a German pathologist

Childhood nephrotic syndrome is primarily steroid-responsive, often characterized by frequent relapses and steroid dependence. Various steroids and synthetic adrenocorticotropic hormone (ACTH) analogs have been utilized since the 1950s [8-16].

Henry Lewis Barnett (Figure 1G) and his team were among the first to explore ACTH and cortisone treatment for nephrotic syndrome in 1950 [8].

Figure-1G: Henry Lewis Barnett (1914-2001), An American pioneer of pediatric nephrology

Gavin Arneil and Wilson reported the effective use of cortisone in 1952 and detailed treatment outcomes for 16 patients in 1953, emphasizing its role in inducing diuresis [10, 11].

By 1954, Lauson et al. noted the positive impact of ACTH on glomerular permeability in childhood nephrotic syndrome.

Gavin Arneil (Figure 1H) was likely the first to report the use of prednisolone for treating nephrotic syndrome in 1956 [13].

Figure-1H: Gavin Cranston Arneil (March 7, 1923-January 21, 2018), a Scottish pioneer of pediatric nephrologist from Glasgow

In 1968, John Stewart Cameron (Figure 1I) demonstrated that the minimal change lesion, the predominant histopathological type in childhood nephrotic syndrome, is the only type that consistently responds to corticosteroid treatment within eight weeks [17].

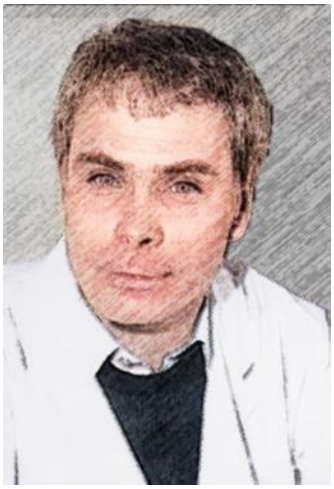

Figure-1I: John Stewart Cameron (July 5, 1934-July 30, 2023), a British nephrologist

Chlorambucil and cyclophosphamide began to be used in the 1970s for challenging cases with significant steroid side effects [19-24].

The 1979 international study of kidney disease involved 54 children with frequently relapsing nephrotic syndrome, revealing that both treatment regimens were inadequate in preventing relapses [25].

Treatment strategies have evolved over the decades, with steroids being the primary therapy. However, issues such as frequent relapses and steroid dependency have led to the exploration of alternative treatments like levamisole and mycophenolate mofetil. Notably, intramuscular ACTH (synacthen) has gained attention for its beneficial effects on glomerular permeability and potential to alleviate psychiatric side effects associated with high-dose steroids.

In 1980, Tanphaichitr et al. highlighted the potential role of T-cell lymphocyte dysfunction in minimal change nephrotic syndrome, employing levamisole, an anthelmintic having immune stimulant property to treat seven children with minimal change nephrotic syndrome during relapses with positive outcomes.

Levamisole was used in a dose of 1.5 to 3.9 mg kg biweekly for one to six months. After Treatment was associated with a complete remission without the occurrence of side effects [26].

In 1984, Patrick Niaudet (Figure 1J) from Paris and his research team reported successful levamisole treatment in children with frequently relapsing nephrotic syndrome, leading to reduced corticosteroid doses without significant side effects [27].

Figure-1J: Patrick Niaudet, a pediatric nephrologist from France

They described the treatment of 30 cases of childhood frequently relapsing nephrotic syndrome with levamisole (2.5 mg/kg twice weekly) for a mean period of 9.9 months. Treatment in sixteen patients enabled marked reduction of corticosteroids without experiencing a relapse. However, levamisole was not effective in 14 patients. Seven patients who responded to levamisole therapy, experienced reduction of neutrophils to below 4×10^9/L. Three patients experienced transient granulocytopenia.

Therefore, Niaudet and his research team suggested that levamisole can be useful option in frequently relapsing nephrotic syndrome, and with minimal side effects [27].

The British Association for Pediatric Nephrology supported levamisole, an immunostimulant agent as an alternative therapy in 1991, confirming its effectiveness in maintaining steroid-free remission.

They reported the treatment of 31 cases of frequently relapsing and dependent steroid nephrotic syndrome with levamisole (2.5 mg/kg on alternate days), while 30 patients received placebo for a maximum of 112 days. In both groups, prednisolone was progressively decreased and was discontinued by 56 days. 14 patients who received levamisole and only four patients who received placebo remained in remission at 112 days (log rank analysis p less than 0.01).The British Association for Pediatric Nephrology considered levamisole to be effective in maintaining a steroid-free remission, and it was not associated with important side effects [28].

Capodicasa et al. in 1986 and Brodehl in 1991 emphasized the possible occurrence of nephrotoxicity during the use of cyclosporine in the treatment of frequently relapsing nephrotic syndrome as evidenced by serum creatinine monitoring [29, 30].

Concerns regarding nephrotoxicity with cyclosporine prompted increased recommendations for levamisole in difficult cases of primary childhood nephrotic syndrome [31-39].

In 1998, Briggs from the United States suggested mycophenolate mofetil as a beneficial steroid-sparing agent for challenging cases of nephrotic syndrome. Mycophenolate mofetil can be used instead of cyclosporine in difficult cases of childhood nephrotic syndrome caused by minimal change disease and possibly by other glomerular disease [40].

Patients and methods

We utilized existing evidence to enhance the management of challenging childhood conditions such as frequently relapsing, steroid-dependent, and steroid-resistant nephrotic syndrome. We previously treated a boy (Figure 2A) with frequently relapsing steroid nephrotic syndrome who faced significant steroid toxicity, resulting in stunted growth due to prolonged high doses of prednisolone (2 mg/kg daily). His treatment involved an alternate-day regimen of levamisole combined with mycophenolate mofetil, significantly reducing the prednisolone dosage and its adverse effects.

This paper describes the use of a new therapeutic approach in the treatment of a second boy who had frequently relapsing nephrotic syndrome that didn't respond to cyclosporine.

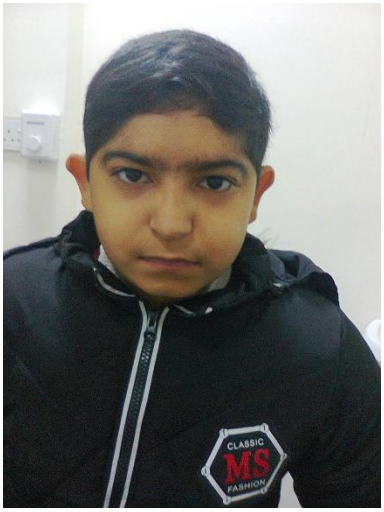

Figure 2A: A boy with frequently relapsing steroid nephrotic syndrome who faced significant steroid toxicity, resulting in stunted growth

Results

The boy first presented with nephrotic syndrome on August 20, 2020, at approximately seven years of age. By July 20, 2024, he was experiencing his seventh or eighth episode and was on oral prednisolone (10 mg daily) and cyclosporine (100 mg daily). His previous relapses had required high-dose prednisone, diuretics, and, at times, intravenous albumin.

Cyclosporine treatment was started before about 14 months. Previous relapses were treated with large dose oral prednisone and diuretics, and sometime he was receiving intravenous infusion of albumin.

His father noted that the use of high-dose prednisone during relapses correlated with depressive symptoms that did not fully resolve with dose reductions.

On July 20, 2024, lab tests revealed normal renal function: serum creatinine at 0.4 mg/dL and blood urea at 25.5 mg/dL, with total serum protein at 4.2 g/dL and serum albumin at 1.5 g/dL. Urine analysis showed 200 mg/dL albumin (normal levels are <2 mg/dL).

The patient was not treated with the traditional large daily dose of prednisone, but he was treated with low-dose prednisolone, intramuscular synacthen (Tetracosactide, 1 mg weekly [Tetracosactride, a synthetic peptide with an amino acid sequence identical to the first 24 amino acids of corticotrophin]), and mycophenolate mofetil, starting at 1000 mg in two divided doses and increasing to 1500 mg daily after one week when urine showed 100 mg/dL albumin.

Prior to starting mycophenolate, complete blood studies indicated normal levels: Hemoglobin at 14.2 g/dL, WBC at 7.2 × 10^9/L, lymphocytes at 3.7 × 10^9/L (47.2%), and platelets at 352 × 10^9/L.

By August 3, 2024, blood tests showed Hemoglobin at 13.4 g/dL, WBC at 7.9 × 10^9/L, lymphocytes at 3.6 × 10^9/L (44.0%), and platelets at 332 × 10^9/L.

On August 17, 2024, the boy has received 5 intramuscular synacthen urine exam showed only trace amount of albumin. Intramuscular synacthen was stopped. Total serum protein was 7.0 g / dL and serum albumin was 4.2 g / d. Figure 2B illustrates the boy on October 12, 2024, with urine tests showing no detectable albumin.

Figure 2B: The boy on October 12, 2024, with urine tests showing no detectable albumin

Discussion

The beneficial effects of ACTH on glomerular permeability in childhood nephrotic syndrome were first reported in 1954 by Lauson et al. Subsequent studies (2004, 2010) indicated that ACTH could improve various nephritic syndromes by protecting podocytes from damage [42-47].

In 2004, Berg and Arnadottir reported that ACTH therapy was associated with improvement in a variety nephritic syndrome [42].

In 2010, the work of Gong and Dworkin suggested that ACTH has a protective effect on podocytes as it can reduce foot-process effacement, podocyte apoptosis, and decrease the decline in glomerular expression of podocyte markers, including nephrin, vimentin, and podocin. Therefore it can have a beneficial effect when used in different types of glomerular disorders [44].

In 2011, Rujun Gong from the United States emphasized the renaissance of corticotropin treatment in nephrotic nephropathies [45].

Chlorambucil and cyclophosphamide and have used as early as the 1970s in difficult cases associated with significant steroid side effects [19-24].

In 1979, Wiggelinkhuizen and colleagues reported the treatment of thirteen childhood cases of frequently relapsing nephrotic syndrome with chlorambucil (Leukeran), a cytotoxic drug in a dose of 0.2 mg/kg/day for eight weeks. Treatment was associated with remission in 11 patients for an average of 31 months. No side-effects of therapy were observed in this study, but several grave complications of high-dosage therapy have been reported in the recent literature [23].

In 1980, Williams et al. reported the treatment of 59 childhood cases of frequently relapsing, steroid dependent and resistant idiopathic nephrotic syndrome with chlorambucil and prednisone for 5 to 15 weeks. 95% of the patients experienced remission at one year and 85% at 4 years. All patients except two experienced remissions lasting longer than steroid-induced remissions. Only eight other patients experienced one or more relapses after treatment [24].

The boy in this report was experiencing steroid-induced behavioral and psychiatric abnormalities mostly in the form of depressive mood.

In 2013, Youssef et al from Egypt reported a study which included thirty children with steroid sensitive nephrotic syndrome who were at remission or were receiving prednisolone in a low dose and experienced relapse. The study showed that prednisolone treatment in high doses was associated psychiatric abnormalities including anxiety and depression [41].

Several studies supported the potential of intramuscular synacthen to have a beneficial effect in childhood nephrotic syndrome [42-47].

Our current study highlights intramuscular synacthen's role in mitigating the psychiatric symptoms associated with high doses of prednisolone.

In 1896, Bartolomeo Gosio (Figure-3) reported the isolation of mycophenolic acid, an antibacterial from the mould Penicillium brevicompactum. The novel compound has an antibacterial property against anthrax bacterium. However, mycophenolic mofetil was not introduced into clinical use.

In 1912, Alsberg and O.M. Black from the United States also reported its isolation.

Mycophenolate mofetil, derived from mycophenolic acid, has been established as a safe and effective treatment for preventing immune rejection in organ transplants [48-50]. It has also shown promise in managing childhood nephrotic syndrome [52-67]

Mycophenolate mofetil (Cellcept), a derivative of mycophenolic acid, and its prodrug was introduced by Anthony Allison a geneticist from South African and his wife Elsie M Eugui during the early 1970s, and has been used as an antimetabolite immunosuppressive agent that work by inhibiting purine synthesis.

Mycophenolic mofetil has been considered safe and useful in preventing the immune rejection of allografts since the early 1990s. Therefore, it has been increasingly used as an anti-rejection agent in organ transplants [48-50].

Figure-3: Bartolomeo Gosio (17 March17, 1863-April 13, 1944), an Italian medical scientist

In 1996, Confavreux and Moreau from France emphasized the available evidence suggesting that mycophenolate mofetil has a good safety profile and lacks mutagenic effect and chromosome breakage [51].

During the previous decades, mycophenolate mofetil has been used extensively with a beneficial effect in childhood nephrotic syndrome [52-68].

In our case, the combination of intramuscular synacthen and oral mycophenolate resulted in successful treatment without significant side effects, effectively minimizing steroid toxicity, particularly concerning psychiatric manifestations.

Conclusion

Childhood nephrotic syndrome remains a complex condition requiring a multifaceted approach to management, particularly in cases that are frequently relapsing or steroid-dependent. The historical evolution of understanding this disorder underscores the significance of ongoing research and innovation in treatment strategies.

The successful use of a combination therapy involving intramuscular synacthen and mycophenolate mofetil in the presented case demonstrates the potential for alternatives to traditional corticosteroid treatments. This approach not only alleviated the nephrotic syndrome symptoms but also mitigated the psychiatric side effects commonly associated with high-dose steroid therapy.

Future research should continue to explore and validate such therapeutic combinations to optimize outcomes for children with challenging nephrotic syndrome, aiming for effective management with minimal adverse effects.

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The author has the copyrights of all the sketches (Figures) included in this paper.

Conflict of interest: None.

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