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Original Research Article

Antiepileptic Drug Induced Renal Complications in Children

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Abstract

Background: Long term used of certain antiepileptic medications (AEDs) by children may experience some renal side effects, including proteinuria, electrolyte imbalance, decreased GFR, nephrolithiasis and renal tubular dysfunction. Monitoring and prevention are aided by knowledge of incidence and risk factors in pediatric practice.

Objective: To outline the Incidence of renal problems linked to AED treatment in a group of children with epilepsy.

Methods: 100 children diagnosed with epilepsy and on AED therapy for ≥6 monthswere enrolled in this cross sectional study. A detailed clinical history regarding AEDs, demographic data and clinical examination findings were recorded. Laboratory investigations related to renal toxicity and renal ultrasound was done. Observed renal complications associated with the AED were recorded and compared with the types of AED used.

Results: The overall incidence of renal complications on children taking long term AED were 26%. The mean age was 9.2 ± 3.1 years; 58 were males and 42 were females. The most commonly used AED was Valproate (32%) followed by Carbamazepine (24%) and Phenytoin (18%). The common complications were Proteinuria (14%), Electrolyte imbalance (12%), and Decreased GFR (10%). Highest frequency of renal complications (37.5%) were associated with the Valproate followed by use of Phenytoin (27.8%).

Conclusion: Renal complications are not uncommon among children receiving AED therapy, with older-generation drugs like valproate and phenytoin showing higher associations. Early detection through routine renal screening is critical to prevent long-term kidney damage.

Keywords: Antiepileptic Drugs, Renal Complications, Children.

Introduction

Epilepsy is a complex chronic neurological illness that affects almost 65 million people worldwide, with children accounting for 20% of those affected [1]. It includes a wide range of seizure types and syndromes, each with a unique prognosis and reaction to treatment. Antiepileptic medication (AED) treatment results in a favorable outcome for most patients in terms of seizure control, however this success is not without side effects. About 25% of patients discontinue their anticonvulsant medication early due to drug side effects, which also have a significant impact on patient compliance [2]. Adverse effect control is crucial for the treatment of epilepsy in children and adolescents, which is often recommended for at least two years (and sometimes for life) [3].Long-term antiepileptic medication (AED) users may experience side effects from the medications as well as other illnesses, which could restrict their use of AEDs [4]. Numerous AEDs are metabolized by the liver and eliminated through urine. Examples of this pharmacokinetics include lamotrigine, phenobarbital, and lacosamide, which are often used in clinical practice. Levetiracetam and topiramate, on the other hand, do not change before being eliminated by urine. Kidney adverse effects may result from long-term usage of certain medications. Nephrotoxicity, calciuria, and other kidney-related problems are among the frequent side effects [5]. Even so, only a small percentage of individuals receiving long-term AED medication go on to develop chronic kidney disease (CKD).Proximal renal tubular dysfunction, Fanconi syndrome, renal tubular acidosis, electrolyte imbalance, and nephrolithiasis are some of the manifestations of renal problems associated with AEDs in children. Valproic acid has been linked to reversible Fanconi syndrome in children, especially

those with neuro-developmental impairments or receiving polytherapy, according to a number of case reports and observational studies[6,7]. Furthermore, topiramate is known to predispose children to nephrolithiasis through its carbonic anhydrase inhibitory activity, while enzyme inducers like carbamazepine and phenytoin may change renal hemodynamics and tubular function [8,9].Because of continuous nephron maturation, increased drug exposure relative to body weight, and the frequent need for polypharmacy in refractory epilepsy, the pediatric population is particularly susceptible to drug-induced kidney impairment. Since most of these side effects can be reversed with timely cessation or substitution of the offending medication, early detection of renal involvement is therefore essential. Additionally, it has been proposed that regular renal function monitoring during AED administration reduces the risk of chronic kidney injury [10].

Aim of the study: The study aimed to evaluate renal complications among children receiving long-term antiepileptic drug (AED) therapy

Materials and Methods

This was a cross-sectional, observational study conducted in the Department of Pediatrics at a tertiary care teaching hospital. A total of 100 children aged between 1 and 16 years who had been receiving one or more AEDs for a minimum duration of six months were enrolled in the study. Participants were recruited from outpatient and inpatient pediatric clinics. Written informed consent was obtained from parents or legal guardians

Inclusion Criteria

- Age range for AED initiation: 1 to 16 years.
- Diagnosed with epilepsy and on AED therapy for ≥6 months
- A minimum of one baseline chemistry test and ≥1 lab or renal imaging follow-up visit
- Parents/guardians who provided written informed consent for the study

Exclusion criteria

- Chronic kidney disease (CKD stage ≥2) that existed prior to starting an AED
- Prior to beginning AED, a structural kidney impairment was documented
- Known systemic diseases affecting renal function
- Parents/guardians who not provided written informed consent for the study

Data Collection: A detailed clinical history was obtained, including age at seizure onset, seizure type, duration of AED use, type and dose of AEDs, and whether monotherapy or polytherapy was being used. Demographic data such as age, gender, and duration of therapy were recorded. Each child underwent a comprehensive physical examination, with particular attention to signs of volume status, hypertension, or edema.

The following investigations were performed for each participant:

- Urinalysis: Dipstick testing and microscopic examination for proteinuria and hematuria
- Spot urine protein-to-creatinine ratio (for quantifying proteinuria)
- Serum creatinine, blood urea nitrogen (BUN) and glomerular filtration rate (eGFR)
- Serum electrolytes (sodium, potassium, calcium)
- Renal ultrasound: To assess kidney size, echogenicity, and presence of nephrolithiasis or structural abnormalities

Definitions of Renal Complications

- Proteinuria: Spot urine protein-to-creatinine ratio ≥0.2 mg/mg
- Hematuria: ≥5 red blood cells per high-power field in microscopic urine examination
- Elevated serum creatinine: >1.2 mg/dL (age-adjusted)
- Reduced eGFR: <90 mL/min/1.73 m²
- Electrolyte disturbances: Serum sodium <135 mmol/L, calcium <8.5 mg/dL
- Nephrolithiasis: Confirmed by renal ultrasound

Drug Classification: AEDs were categorized into monotherapy or polytherapy. Individual drugs included valproate, phenytoin, carbamazepine, and levetiracetam. Polytherapy was defined as the use of two or more AEDs simultaneously for seizure control.

Statistical Analysis: Data were analysed by using SPSS version 25. Descriptive statistics (mean ± SD or median [IQR]; counts and percentages). Comparisons by t-test and chi-square are exact. Variables with $p<0.10$ on univariate analysis entered into multivariable logistic regression. A $P<0.05$ was considered statistically significant.

Results

A total of 100 children on long-term antiepileptic therapy were studied. The mean age was 9.2 ± 3.1 years; 58 were males and 42 were females. The mean duration of AED therapy was 3.8 ± 2.2 years [Table: 1].

Table 1: Demographic Characteristics of Study Population (n=100)

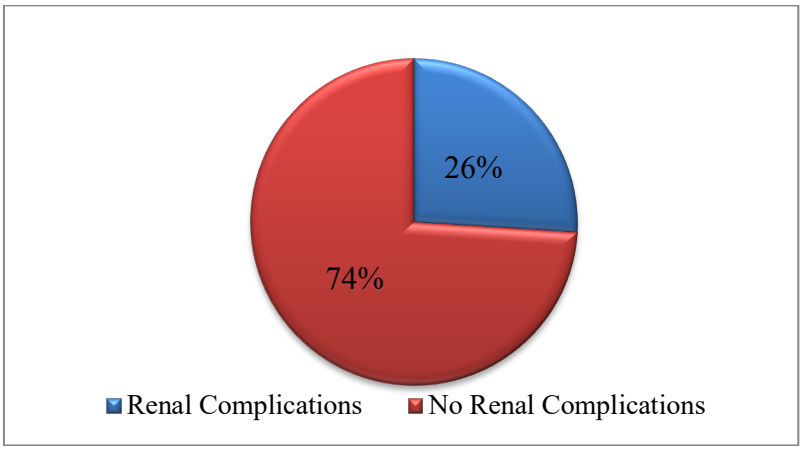
Characteristic	Value (mean ± SD)
Mean Age (years)	9.2 ± 3.1
Age range	3 – 16 years
Male: Female	58: 42
Duration of AED therapy	3.8 ± 2.2 years

The most commonly used AED was Valproate (32%) followed by Carbamazepine (24%) and Phenytoin (18%). [Table: 2].

Table 2: Frequency of Antiepileptic Drugs Used in study patients

Antiepileptic Drugs	Number	Percentage (%)
Valproate	32	32%
Carbamazepine	24	24%
Phenytoin	18	18%
Levetiracetam	16	16%
Polytherapy (≥2 drugs)	10	10%

The overall incidence of renal complications on children taking long term AED were 26%



Graph 1: Incidence of AED induced Renal Complications among study children

The common complications were Proteinuria (14%), Electrolyte imbalance (12%), Decreased GFR (10%), Microscopic hematuria (8%), Elevated serum creatinine (6%), Nephrolithiasis (by USG) (4%) and other renal complications were 26%.

Table 3: Types of Renal Complications Observed

Renal Complications	Frequency	Percentage (%)
Proteinuria	14	14%
Electrolyte Imbalance (Hyponatremia, Hypocalcemia)	12	12%
Microscopic Hematuria	8	8%
Elevated Serum Creatinine	6	6%
Decreased GFR (<90 ml/min/1.73 m²)	10	10%
Nephrolithiasis (by USG)	4	4%
Other Renal Complication	26	26%

Highest frequency of renal complications (37.5%) associated with the Valproate followed by used of Phenytoin (27.8%). Details descriptions renal complications associated with the AED were shown in table: 4.

Table 4: Association of Renal Complications with Type of AED

Antiepileptic Drugs	Used frequency	Renal complication (%)
Valproate	32	12 (37.5%)
Carbamazepine	24	4 (16.7%)
Phenytoin	18	5 (27.8%)
Levetiracetam	16	2 (12.5%)
Polytherapy (≥2 drugs)	10	3 (30%)

Discussion

In this study of 100 pediatric patients on long-term antiepileptic therapy, renal complications were observed in 26% of participants. The most frequent renal abnormalities included proteinuria (14%), electrolyte disturbances (12%), decreased estimated glomerular filtration rate (eGFR; 10%), and microscopic hematuria (8%). These findings underscore the potential nephrotoxic effects of chronic AED use in children.

Our results align with prior research suggesting that certain AEDs, particularly valproate and phenytoin, may pose a higher risk for renal involvement. Valproate, used by 32% of patients in our cohort, was associated with the highest frequency of renal complications (37.5%). This supports findings by Guo et al [11], who reported increased urinary protein excretion and reduced renal function markers in children on long-term valproate therapy.

The mechanism is thought to involve mitochondrial toxicity and interference with fatty acid metabolism, contributing to proximal tubular dysfunction (Zhao et al) [12].

Phenytoin, another older AED, was associated with renal complications in 27.8% of its users in our study. Phenytoin's nephrotoxicity may be mediated via oxidative stress and induction of inflammatory pathways, as reported by Mahmoud et al [13]. Carbamazepine, used by 24% of our cohort, was associated with a lower complication rate (16.7%), although previous reports have described rare cases of interstitial nephritis and hyponatremia with its use (Reid et al) [14].

Polytherapy was also associated with increased risk (30%), which is consistent with the concept that drug interactions and cumulative toxicity may exacerbate renal effects. A study by Verrotti et al [15] also emphasized that AED polytherapy is more likely to impair tubular function than monotherapy, particularly with combinations involving valproate or older-generation AEDs. Electrolyte abnormalities were noted in 12% of patients, most commonly hyponatremia and hypocalcemia. Hyponatremia has been frequently reported in association with carbamazepine and oxcarbazepine due to their antidiuretic hormone-like effects (Lucey JV. et al) [16].

Although not directly nephrotoxic, these disturbances can reflect subtle renal tubular effects and warrant regular biochemical monitoring. Interestingly, levetiracetam, a newer-generation AED, was associated with the lowest complication rate (12.5%). This aligns with Glauser T. et al [17] supporting its favorable renal safety profile. Nevertheless, isolated reports have emerged describing levetiracetam-induced interstitial nephritis, Shukla A. et al [18] indicating that even newer drugs are not without risk.

Renal ultrasound revealed nephrolithiasis in 4% of patients, all of whom were on valproate. Valproate has been associated with hypocitraturia and hypercalciuria, promoting stone formation (Kozeny et al) [19].

Taken together, these findings reinforce the need for regular renal monitoring in children on long-term AED therapy, especially when using valproate, phenytoin, or in cases of polytherapy. Urine analysis, serum creatinine, electrolyte levels, and eGFR should be part of routine follow-up to detect early signs of renal dysfunction.

Conclusion

Renal complications are not uncommon among children receiving AED therapy, with older-generation drugs like valproate and phenytoin showing higher associations. The common complications were Proteinuria, Electrolyte imbalance, renal tubular dysfunction, microscopic hematuria and Nephrolithiasis. Early detection through routine renal screening is critical to prevent long-term kidney damage. To establish evidence-based monitoring techniques and ascertain the true incidence, larger prospective pediatric studies are required.

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