International Journal of Contemporary Pediatrics
Mir ZA et al. Int J Contemp Pediatr. 2026 Feb;13(2):176-179
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20260085

Original Research Article

Incidence of hypocalcemia in pediatric patients with Down syndrome: a prospective observational study

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Received: 04 May 2025
Revised: 02 December 2025
Accepted: 31 December 2025

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ABSTRACT

Background: Down syndrome (DS) is the most frequently occurring chromosomal condition, affecting from 1 in 700 to 1 in 1,500 live-born babies. Children with DS are at high risk of developing metabolic and endocrine abnormalities such as thyroid dysfunction, diabetes mellitus, obesity, short stature, vitamin D deficiency, low bone mineral density, and gonadal dysfunction than the general population. However, the prevalence and persistence of hypocalcemia in early childhood remain underexplored. This study aimed to assess the incidence and significance of hypocalcemia in pediatric patients with DS aged 1 to 5 years.
Methods: A prospective observational study was conducted on 55 children with genetically confirmed DS, aged 1 to 5 years. Serum calcium, phosphate, and parathyroid hormone (PTH) levels were measured at baseline and followed up for over 12 months. Vitamin D levels and dietary calcium intake were also assessed. Statistical analysis was performed to compare hypocalcemia prevalence with general pediatric population data.
Results: Hypocalcemia (serum calcium <8.5 mg/dl) was observed in 21 out of 55 children (38.2%), which was significantly higher than in the general pediatric population ($p<0.001$). Hypoparathyroidism was identified in 11 cases (20%), with persistently low PTH levels. Vitamin D deficiency was present in 27 children (49%), contributing to secondary hypocalcemia in some cases. Clinical symptoms: Hypotonia (35%), delayed motor milestones (22%), and seizures (7%).
Conclusions: Hypocalcemia is significantly more prevalent in children with DS aged 1 to 5 years, with hypoparathyroidism and vitamin D deficiency being major contributing factors. Routine screening and early calcium and vitamin D supplementation may help prevent complications in this vulnerable population.

Keywords: Down syndrome, Hypocalcemia, Hypoparathyroidism, Vitamin D deficiency, Pediatric endocrinology

INTRODUCTION

Down syndrome (DS), the most frequently occurring chromosomal condition, affects approximately 1 in 700 live births worldwide.[1,2] DS is associated with a variety of metabolic and endocrine abnormalities, including thyroid dysfunction, obesity, and hypocalcemia.[3] While thyroid dysfunction has been extensively documented in DS, disturbances in calcium homeostasis remain less explored.[4] Hypocalcemia, defined as a serum calcium level below the age-appropriate reference range, can result from hypoparathyroidism, vitamin D deficiency, or inadequate dietary calcium intake.[5]

In pediatric populations, hypocalcemia can contribute to hypotonia, developmental delays, muscle cramps, and seizures, further compounding the neurological and developmental challenges in DS.[6,7]

Hypoparathyroidism, a recognized endocrine abnormality in DS, may lead to hypocalcemia due to reduced PTH secretion, resulting in decreased calcium reabsorption and increased phosphate retention.[6] Elevated serum phosphate levels can exacerbate hypocalcemia, increasing the risk of seizures, particularly in infants and young children with DS.[7]

Despite established associations between DS and endocrine disorders, the specific incidence and risk factors for hypocalcemia in pediatric DS populations remain underexplored. Prior studies have suggested a higher prevalence of hypoparathyroidism and vitamin D deficiency in DS, both potential contributors to hypocalcemia.[6] This study aims to systematically evaluate the incidence of hypocalcemia in pediatric patients aged 1-5 years with DS and identify potential clinical and demographic correlates, such as hypotonia, delayed milestones, and seizures.

METHODS

This prospective observational study was conducted over 12 months, from June 2023 to June 2024, at the department of pediatrics and neonatology (OPD and IPD), SKIMS, Srinagar. Ethical approval was obtained from the institutional ethics committee (SIMS/PED/2023-103 dated 19-05-2023). Fifty-five children aged 1-5 years with karyotype-confirmed DS were recruited using a convenience sampling technique. Children with chronic kidney disease, severe malnutrition, or medication affecting calcium metabolism were excluded.

Demographic data, clinical history, and relevant biochemical parameters (serum calcium, phosphate, alkaline phosphatase, PTH, and 25-hydroxyvitamin D levels) were collected. Neurological findings, including hypotonia, developmental delays, and seizure history, were also documented.

Blood samples were obtained after an overnight fast to minimize diurnal variations in calcium levels.[8]

Hypocalcemia was defined as serum calcium levels <8.5 mg/dl, corrected for albumin using the formula: Corrected Ca (mg/dl)=Total Ca (mg/dl)+0.8×(4- serum albumin in g/dl).[9]

Vitamin D deficiency was defined as 25(OH)D levels <20 ng/ml.[10] Hypoparathyroidism was identified by low PTH levels in the presence of hypocalcemia and hyperphosphatemia.[7]

Sample size calculation

The sample size for this prospective observational study was not pre-calculated, as the study was conducted over a fixed 12-month period (June 2023 to June 2024). During this period, a total of 55 children with karyotype-confirmed DS, aged 1-5 years, were enrolled based on availability and eligibility criteria. All eligible children who presented to the pediatric and neonatology departments during the study period and met the inclusion criteria were included in the study

Statistical analysis

Data were analyzed using SPSS software version 19.0 (IBM Corp.). Chi-square and Fisher's exact tests were applied, with $p<0.05$ considered statistically significant.

RESULTS

Out of 55 children with DS, 21 (38.2%) had hypocalcemia, significantly higher than the general pediatric population ($p<0.001$). Hypoparathyroidism was observed in 11 children (20%), confirmed by low PTH levels, while 27 children (49%) exhibited vitamin D deficiency. Hypotonia was documented in 19 children (35%), delayed motor milestones in 12 children (22%), and seizures in 4 children (7%).

Table 1: Gender distribution of children with DS enrolled in the study.

Variables	Total	Hypocalcemic	Percentage
Male	28	12	42.8%
Female	23	9	39.1%

The 42.8% of children with DS were male gender where as 39.1% were female gender.

Table 2: Age distribution of the patients DS and hypocalcemia.

Age group (in years)	Total cases	Hypocalcemia	Percentage
1-2	11	5	45.4%
2-3	16	7	43.7%
3-4	13	5	38.4%
4-5	15	4	26.6%
Total	55	21	38.2%

Hypocalcemia was more prevalent in the lower age groups.

Table 3: Prevalence of hypocalcemia in pediatric DS patients vs. general population.

Groups	Total cases	Hypocalcemia	Percentage	P value
Pediatric DS (1-5 years)	55	21	38.2%	<0.001
General ped. population (1-5 years)	-	-	~3%	-

Prevalence of hypocalcemia was significantly greater in children with DS (38.2%) than that of general population (almost 3%), p<0.001.

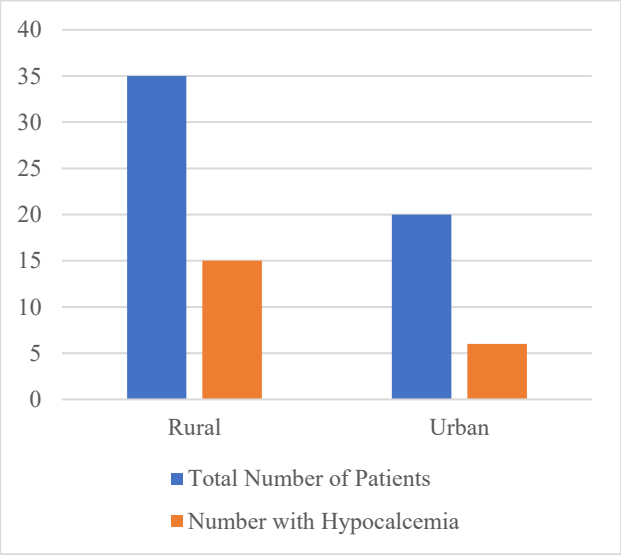

Figure 1: Demography of the patients with DS and hypocalcemia.

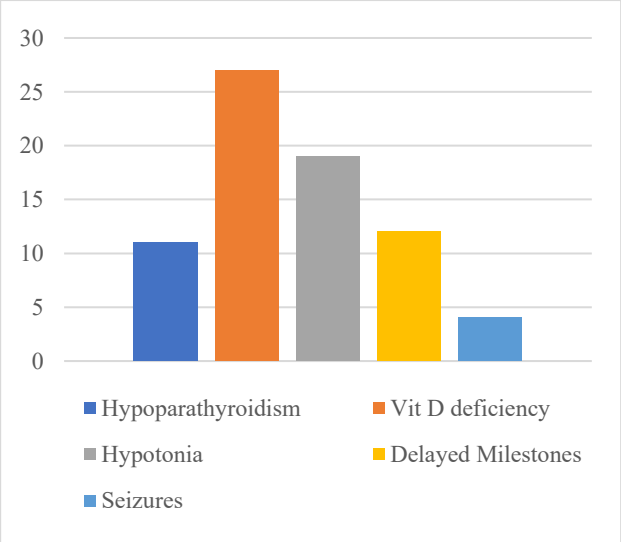

Figure 5: Other biochemical and clinical manifestations in children with DS in our study.

Apart from hypocalcemia, rickets was more prevalent among other biochemical and clinical manifestation, followed by hypotonia, delayed milestones, hypoparathyroidism and seizures.

DISCUSSION

The observed incidence of hypocalcemia (38.2%) in this pediatric DS cohort is substantially higher than the reported incidence in age-matched general pediatric populations (~3%). This finding aligns with previous studies that have identified a higher prevalence of metabolic and endocrine abnormalities in children with DS, as highlighted by Guaraldi et al.[6]

Hypoparathyroidism, present in 20% of cases, suggests a potential developmental anomaly of the parathyroid glands in DS. Guaraldi et al previously reported that parathyroid gland hypoplasia or dysfunction might be a consequence of trisomy 21, leading to impaired PTH secretion and subsequent hypocalcemia.[6] Furthermore, the pathophysiological mechanism underlying hypoparathyroidism in DS may involve genetic, autoimmune, and structural factors, all of which warrant further investigation.

Vitamin D deficiency, identified in 49% of participants, further exacerbates the risk of hypocalcemia. This finding aligns with studies by Santos et al and Holick et al which reported that children with DS are more susceptible to vitamin D deficiency due to factors such as decreased outdoor activity, dietary insufficiencies, and altered vitamin D metabolism.[11,12] The high prevalence of vitamin D deficiency underscores the need for targeted nutritional interventions, particularly given the established role of vitamin D in calcium homeostasis.

Children with hypocalcemia exhibited symptoms such as hypotonia, muscle cramps, and developmental delays, which are clinical manifestations commonly associated with hypocalcemia. Feigerlova and Kelly emphasized that these symptoms could significantly impact motor and cognitive development in DS, reinforcing the need for early screening and intervention.[9] Additionally, Roizen and Patterson emphasized the importance of monitoring calcium and vitamin D levels in DS patients to prevent neurological sequelae.[8]

Comparison with other studies reveals that the incidence of hypocalcemia observed in the present study is higher than that reported by Feigerlova et al who documented a 15% incidence of hypocalcemia in a similar cohort of DS children.[9] However, the higher incidence in our study may be attributable to differences in study design, inclusion criteria, or regional dietary patterns. Moreover, Parker et al reported a similar prevalence of hypoparathyroidism in DS patients, suggesting that the genetic underpinnings of DS may predispose patients to parathyroid insufficiency.[7]

Limitations

The study's sample size was relatively small, and data collection was limited to a single center, potentially limiting generalizability. Additionally, the absence of a control group without DS precludes a direct comparison of hypocalcemia incidence.

CONCLUSION

This study identifies a statistically significant association between DS and hypocalcemia in pediatric patients aged

1-5 years. Given the high prevalence of hypoparathyroidism and vitamin D deficiency, regular monitoring of calcium and vitamin D levels in pediatric DS patients is recommended to prevent complications and support early development.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Mir ZA, Rafiq DQ, Mehroosh M, Rashid KW. Incidence of hypocalcemia in pediatric patients with Down syndrome: a prospective observational study. Int J Contemp Pediatr 2026;13:176-9.