Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

The interplay of immunity and growth: a case of combined variable immunodeficiency and growth hormone deficiency

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Introduction: Common variable immunodeficiency (CVID) is one of the more common immunodeficiencies seen in clinical practice with a complex disease pathology; while growth hormone deficiency (GHD) is a disorder characterized by complete or relative absence of the human growth hormone.

Case presentation: This case report presents a 13-year-old female patient with a long history of recurrent respiratory tract and ear infections, along with a notable failure to hit her developmental milestones early in the second decade of her life. The diagnosis was based on a thorough investigation of serum immunoglobulins for CVID and a GH stimulation test for GHD. For these, the patient was placed on a tailored regimen of IVIGs, somatropin therapy, and antibiotics for the recurrent infections.

Case discussion: CVID patients characteristically present with recurrent respiratory and ear infections, showing a marked decrease in immunity. Often diagnosed in childhood, GHD typically presents as growth failure along with developmental delays in dentition. There has been a notable rise in the coexistence of immunodeficiency syndromes and endocrinopathies studied in the past few decades. The case highlights and discusses the complex underlying pathology at play that links the two conditions to each other, while also excluding the various differentials.

Conclusion: The report highlights the various challenges faced by both clinicians and patients when dealing with dual health conditions that may have a relatively nonspecific presentation. Some of which include the diagnostic difficulties, financial strains on the patient leading to poor follow-up, and in the long-term, the development of various complications. This emphasizes the importance of early disease diagnosis and strict management protocols for the said disease, for the overall betterment of the patient's quality of life.

Keywords: antipituitary antibodies, case report, common variable immunodeficiency, growth hormone deficiency, immunoglobulin therapy, recurrent infections

Introduction

Common variable immunodeficiency (CVID) is a primary immunodeficiency disease characterized by hypogammaglobulinemia of namely IgG, IgA, and/or IgM, T-cell dysfunction, and a myriad of clinical features[1,2]. Primary immunodeficiency disorder/diseases (PIDD) are a large group of heterogenous disorders resulting from defects in the development of the immune system and/or its function[1,3]. CVID is associated with severe outcomes such as infections, granulomatous disease, autoimmunity, organ-specific immunopathology, and even

HIGHLIGHTS

- The coexistence of combined variable immune deficiency (CVID) and growth hormone deficiency (GHD) diseases in the same patient is relatively rare and understudied in the literature.
- A 13-year-old female was diagnosed with CVID and GHD based on detailed clinical history.
- The IVIG and somatropin therapy were initiated, and the vitamin D deficiency was corrected in the patient.
- Numerous differentials were ruled out, including protein-losing enteropathy (PLE), and deficient anterior pituitary with common variable immune deficiency (DAVID) syndrome.
- This case serves as an excellent illustration of the challenges faced by both the patient, who must follow a lifelong, multidisciplinary treatment, and the doctor, who must promptly diagnose and manage such complex dual health conditions, requiring meticulous care regimens and regular follow-up.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this articles.

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Annals of Medicine & Surgery (2024) 86:6859–6864

Received 27 June 2024; Accepted 23 September 2024

Published online 30 September 2024

http://dx.doi.org/10.1097/MS9.0000000000002623

malignancy[4]. It would, therefore, be better to call it a 'clinical syndrome' rather than a disease that encompasses a family of disorders with a common phenotype.

The human growth hormone (hGH) is a peptide hormone secreted by the anterior pituitary responsible for growth and development starting from embryonic life and moving on to adulthood. Growth hormone deficiency (GHD) is a disorder characterized by short stature or dwarfism that is proportional. It can be congenital or acquired. Diagnosis can be difficult in young children as the disease may go unnoticed. Cases of CVID and GHD have been previously noted in very few cases worldwide[5–7]. There is much debate as to whether GHD is isolated or presenting itself as an autoimmune pathology due to antipituitary antibodies (APA) in CVID. In this paper, we present a case of a young female patient first diagnosed with CVID within the first decade of her life with a subsequent diagnosis of GHD.

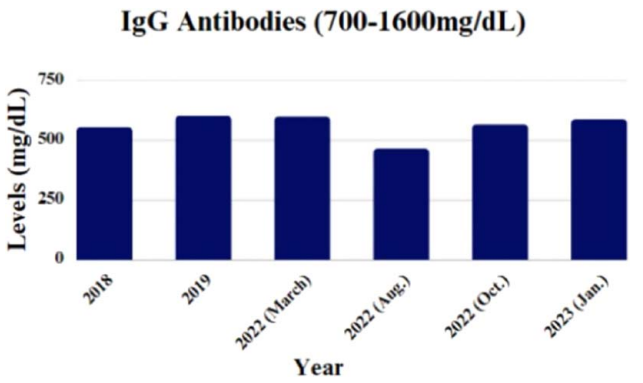

Figure 1. Fluctuations in IgA antibodies, remaining below normal range over the past 5 years.

Case presentation

The clinical scenario is of a 13-year-old female patient with the current working diagnosis of common variable immunodeficiency (CVID) and growth hormone deficiency (GHD). At the age of 8, the patient presented with recurrent bilateral mucopurulent ear discharge. She was diagnosed with acute bilateral osteomastoiditis, with partial erosion of the ear ossicles in the right ear. She also had a history of frequent common colds. On suspicion of an immunodeficiency, hematological investigations were performed to check her serum immunoglobulins and CD cells. The levels of both the immunoglobulins, all three isotypes, and CD3 were below normal; IgG standing, and at 553 mg/dl (700–1600 mg/dl), IgA at 37 mg/dl (70–400 mg/dl), and IgM at 23 mg/dl (40–230 mg/dl); and CD3 and T cells at 930/41.3% (60–76%). Her probable diagnosis at the time was CVID and she was started on IVIG (intravenous immunoglobulins). A year later, in 2019, the patient was also given a preliminary diagnosis of 'a less profound' SCID (severe combined immunodeficiency). However, due to the unavailability of comprehensive genetic panel testing at the hospital, further genetic analysis to confirm or rule out specific genetic mutations associated with SCID was not possible. Nonetheless, the diagnosis was ultimately ruled out through clinical assessment. Key diagnostic tests included the evaluation of immunoglobulin levels (IgG, IgA, and IgM) to assess the humoral immune response[8]. The absence of significant deficiencies in immunoglobulins, coupled with consideration of the patient's clinical presentation, ultimately led to ruling out SCID clinically. Another differential excluded during the same time was DAVID syndrome, which combines CVID with an ACTH deficiency. Early morning blood samples were taken to measure cortisol levels, which came out to be normal at 10 mcg/dl. As no clinical symptoms of ACTH deficiency were observed, DAVID syndrome was ruled out as well. A blood test was performed again that same year revealing a similar picture with even lower IG and CD cell levels. A chest HRCT performed in the same year revealed signs of bronchiectasis, characterized by thickening of the bronchial walls. As mentioned, the patient had had a history of frequent common colds, since the age of 2 years, presenting with cough and fever, leading to one prior hospitalization for pneumonia. The recurrent colds were accompanied by loose stools that also had mucus. The stool, however, returned to normal by the time she was 4 years old. A comparative study of the various IG isotypes over the past years showed a concerning decline (Figs 1 and 2).

She had difficulty gaining weight and possessed a considerably short stature for her age with brachydactyly in four of her fingers and clinodactyly in her fifth finger. She was also noted to have an abnormal dentition, with the normal eruption of permanent teeth but delayed shedding of primary dentition. There were no notable developmental delays otherwise in her earlier years. There were no signs of cognitive impairment, no visual or auditory disturbances, and no history of seizures. Even though the patient was within the mean age range for the onset of pubertal development, her physical characteristics were more comparable to that of a 10-year-old, rather than a 13-year-old. Consequently, GHD was suspected, and further investigations were needed. In the investigative process for GHD, assessing IGF-1 levels aids in evaluating the long-term production of growth hormone, while a pituitary MRI is essential for visualizing the pituitary gland, responsible for regulating growth hormone secretion. These diagnostic procedures play a vital role in determining the underlying cause and severity of GHD. But because of certain limitations within the hospital settings, including unavailability of resources and other necessary equipment, tests to measure IGF1 levels and a pituitary MRI could not be done. Therefore, only a growth hormone stimulation test was feasible for

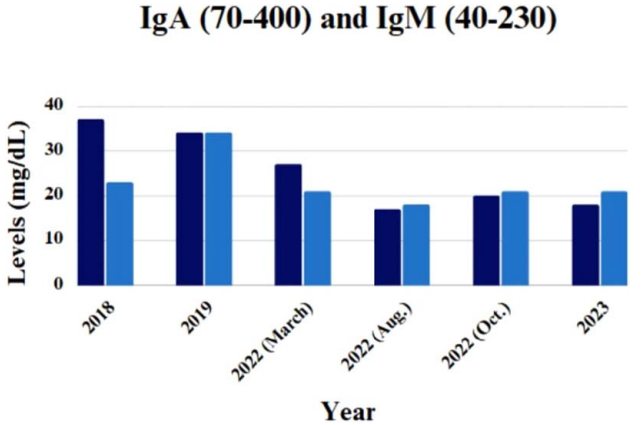

Figure 2. The levels of IgA and IgM antibodies remaining consistently below normal over the past 5 years (2018–2023).

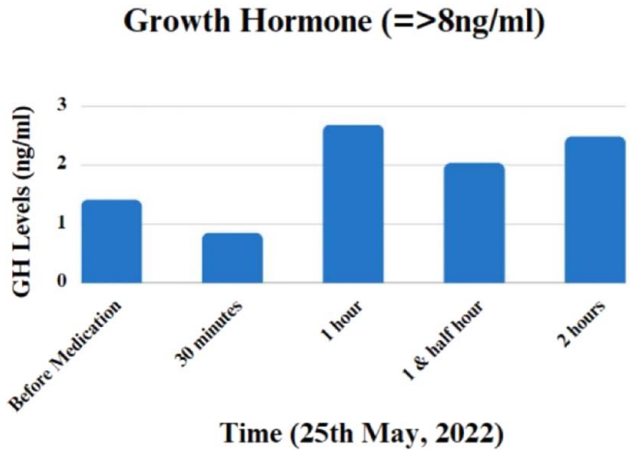

Figure 3. Results of the GH stimulation test after medication (25th May 2022).

confirming the diagnosis under the given circumstances. An IV line was inserted to draw blood and test GH levels preinjection. GH levels taken at 10 h before medication were measured at 1.41 ng/ml (normal > 8 ng/ml), arginine was administered, and GH levels were taken at half an hour, 1 h, 1 and half hours, and 2 h postadministration with levels at 0.847 ng/ml, 2.68 ng/ml, 2.03 ng/ml, and 2.48 ng/ml, respectively, thus confirming the diagnosis (Fig. 3). The patient was then started on GH therapy, Somatropin 600 µg daily, for GHD in May 2022.

In November of 2022, during a routine examination, the patient was found to have abnormally low levels of Vitamin D, 9.11 ng/ml, and a severe deficiency (normal 30–100 ng/ml). For this, the patient was started on vitamin D therapy with a daily dosage of 1500 units for a duration of 6 months. Following this discovery, a thorough clinical assessment was conducted to identify any characteristic features of vitamin D deficiency. Upon examination, typical symptoms associated with severe vitamin D deficiency, such as skeletal abnormalities like rickets, muscle weakness, bone pain, hair loss, loss of appetite, and impaired wound healing, were not observed in the patient. Further investigation was also done to rule out any of the etiological causes leading to vitamin D deficiency, like decreased dietary intake/sun exposure, kidney or liver failure, and increased liver catabolism due to any medications being administered[9]. However, there were no outcomes that could result in such a deficiency. After the correction of vitamin D levels, the patient was re-evaluated during the follow-up and levels stayed stable beyond this, hence any further investigation seemed unwarranted.

In January of 2023, after around 6 months of therapy, the patient presented with a complaint of uniform abdominal distention, beginning initially in the upper abdomen, and then extending to the lower region. An ultrasound scan of the abdominal region and an radiograph of the chest with the abdomen did not reveal any abnormalities. Laboratory studies showed a white blood cell count of 8.7×10^3/µl with 67% neutrophils, a hemoglobin of 10.3 gm/dl, and a hematocrit of 32.2%. Her electrolytes, liver function tests, and renal function tests were all within normal limits. A pediatric surgery consult was sought out and oral contrast study was performed to look for mobility and to rule out any obstructions. Results were normal, and no anomalies were found. This episode of abdominal distention eventually subsided on its own, as recorded in February of 2023. The patient's condition was suspected to be linked to the potential decrease in combined T and B cells, resulting in reduced levels of immunoglobulins in the bloodstream. To confirm this, serum immunoglobulins, IgG, IgA, and IgM, were measured once again, the results which were 586 mg/dl, 18 mg/dl, and 21 mg/dl, respectively, shown in Figures 1 and 2. This immunodeficiency made the patient more susceptible to developing bronchiectasis due to recurrent infections, a known comorbidity associated with CVID.

Discussion

CVID is a complex disorder that can present with a wide range of clinical manifestations, making the diagnosis challenging. This report aims to highlight such challenges, on both the clinician's and the patient's part, in cases such as this, where one may be dealing with complex dual health conditions.

CVID's differentials include other secondary hypogammaglobulinemias. These can be because of conditions leading to either decreased production, like in the case of immunosuppressants, malignancy like leukemia, lymphoma, and multiple myeloma, or increased loss, like in the case of protein-losing enteropathy, or other primary hypogammaglobulinemias like specific IgG1 deficiency, etc., all of which were ruled out either clinically or through investigation deficit in anterior pituitary function and variable immune deficiency (DAVID) is another such differential which was ruled out[10]. DAVID syndrome is a condition characterized by adrenocorticotropic hormone (ACTH) deficiency and primary hypogammaglobulinemia, namely, CVID. It is due to heterozygous mutations of the nuclear factor kappa-B subunit 2 (NFKB2) gene. While the patient has a very similar clinical picture to that of DAVID syndrome, an ACTH deficiency has been ruled out already. The symptoms may include nonspecific ones like hypoglycemia, fatigue, nausea and vomiting, weight loss, and so on, in addition to the features of CVID[11].

Recurrent infections, such as respiratory infections, ear infections, and sinusitis, are the most common clinical features of CVID[12,13]. In the case discussed, the patient presented with recurrent bilateral mucopurulent ear discharge, which is a common symptom of chronic otitis media and osteomastoiditis, often associated with impaired immunity. The most probable immunodeficiencies that lead to increased otitis media are humoral immune deficiencies. Specifically, individuals unable to produce antibodies against encapsulated organisms are at greater risk. Proper management of otitis media in CVID patients is crucial to prevent long-term hearing impairment and ear damage[14].

Frequent respiratory tract infections are a hallmark of CVID and can be caused by bacteria, viruses, or fungi. In addition to ear infections, the patient's medical records indicate a significant medical history of recurrent rhinitis and pneumonia. The persistence of rhinitis, particularly at an early age, raises noteworthy concerns. Additionally, bronchiectasis was detected in the patient's chest HRCT. Bronchiectasis is a common complication of CVID that occurs when the bronchial walls become thickened and dilated. The interrelationship might be due to the recurrent respiratory tract infections, which are typical of CVID that can lead to chronic inflammation and damage to the lungs, resulting in the development of bronchiectasis. The best imaging tool to diagnose and monitor bronchiectasis in CVID patients is an

HRCT scan, where it usually appears cylindrical, bilateral, and diffuse in the middle or lower lobes, and less commonly, in the upper lobes. Although isolated deficiencies of immunoglobulin A (IgA) or immunoglobulin M (IgM) are not typically considered to be related to bronchiectasis, selective deficiencies of immunoglobulin G (IgG) subclasses, specifically IgG2, have been associated with an increased susceptibility to respiratory infections and subsequent development of bronchiectasis. Hence, the incidence of bronchiectasis in patients with common variable immunodeficiency (CVID) ranges from 17 to 76%. The presence of bronchiectasis, however, predisposes patients to further infections, leading to a vicious cycle of chronic lung disease[15,16].

Gastrointestinal symptoms serve as the initial indicator of CVID in ~3% of patients[17]. Almost half of all individuals diagnosed with CVID are affected by some form of gastrointestinal distress. Notably, 21–57% of individuals with CVID report experiencing either transient or persistent diarrhea[16,17]. Usually, patients with CVID have a higher prevalence of gastro intestinal infections due to the inability to produce sufficient IgA antibodies in the gut mucosa. As we can see, in our patient's situation, the recurrent rhinitis was also accompanied by mucosal diarrhea. While the stools returned to normal by the time the patient was 4, it is possible that the patient's gut microbiota, which plays an essential role in the maturation of the immune system, may have been altered, leading to immune dysregulation, malabsorption, and other gastrointestinal symptoms, including loose stools with mucous. Therefore, in patients suspected of immunodeficiency, displaying chronic diarrhea, the immune system should be comprehensively evaluated by measuring serum immunoglobulin levels, assessing antibody function, and enumer ating B and T-cell subsets.

The diagnosis of GHD in this patient further complicates the clinical picture, as growth hormone plays a crucial role in regulating growth and development, and its deficiency can lead to growth failure, increased body fat, and decreased bone density. The fact that the patient exhibits delayed puberty and physical traits resembling those of a 10-year-old rather than a 13-year-old implies that growth hormone deficiency (GHD) may have been present from an early age and may have contributed to the patient's shorter stature. Delayed pubertal growth is a condition in which a child's physical and sexual development lags that of their peers. Children with CVID may experience delayed puberty growth because of immunodeficiency in the body's endocrine (hormonal) system. The hormonal pathway that triggers puberty involves a complex interplay of several hormones, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone (in males), and estrogen (in females). Deficiency in these hormones or their receptors, as can occur in CVID, may impair puberty growth and development. Apart from hormonal deficiency, chronic inflammation, and malnutrition, which are common features of CVID, can also affect puberty growth[18,19].

Low levels of growth hormone can also cause abnormal distribution of body fat, leading to changes in body shape and abnormal bone development, which also accounts for the patient's brachydactyly and clinodactyly. The patient also exhibited an abnormal dentition, with normal eruption of permanent teeth but delayed shedding of primary dentition. This may be attributed to the fact that individuals affected with growth hormone deficiency (GHD) frequently present with dental anomalies, including impaired tooth development, enamel hypoplasia, and delayed tooth eruption. This deviation from normal dental development is because of the critical role that growth hormone plays in the maturation of teeth and their subsequent eruption[18,20]. Skeletal abnormalities are another complication of CVID that may affect growth and development. The skeleton is a dynamic organ that undergoes continuous remodeling and growth throughout childhood and adolescence. Bone formation and mineralization are regulated by several hormones, including growth hormone, insulin-like growth factor 1 (IGF-1), and estrogen and testosterone. In CVID, the chronic inflammation and malnutrition that are present can disturb the balance of these hormones and lead to skeletal abnormalities.

The correlation between CVID and GHD remains unclear; however, a plausible explanation for their connection could be attributed to the involvement of insulin-like growth factor 1 (IGF-1) in the pathogenesis of both conditions. Growth hormone stimulates IGF-1 production, which is crucial in the regulation of immune function. IGF-1 enhances the proliferation and function of T cells, which helps to fight infections. It is possible that the low levels of growth hormone in the patient with GHD are resulting in low levels of IGF-1, which may be affecting their immune function and susceptibility to infections such as rhinitis and otitis media. Another possible explanation is the role of the thymus gland, which is involved in the development of T cells. In CVID, the thymus gland may not function properly, leading to a decreased production of T-cells and a weakening of the immune system[21]. Additionally, vitamin D deficiency has been associated with reduced insulin-like growth factor 1 (IGF-1) levels, a hormone stimulated by GH and essential for growth and development. Vitamin D deficiency may impair the secretion of GH from the pituitary gland. Since GH stimulates the liver to produce IGF-1, reduced GH secretion could lead to lower levels of IGF-1. Furthermore, both vitamin D and GH deficiency play critical roles in skeletal development and maintenance, and deficiencies in either can impact bone mineralization and growth. Therefore, optimizing vitamin D levels may be particularly important for individuals with GH deficiency to support bone health and growth. Overall, while there may be indirect connections and interactions between these conditions, further research is needed to fully understand the nature of these relationships and their clinical implications. Without extensive testing facilities, it might be challenging to determine the precise relationship between CVID, GH deficiency, and vitamin D deficiency in an individual case. Some studies have suggested that vitamin D deficiency may be more prevalent in individuals with CVID, potentially due to immune dysregulation affecting vitamin D metabolism. CVID patients may also have gastrointestinal issues that could lead to malabsorption of nutrients, including vitamin D, resulting in vitamin D deficiency. While there is no direct causative link established between vitamin D deficiency and CVID, maintaining optimal vitamin D levels may support immune function and potentially reduce some symptoms associated with CVID[22–24].

Currently, the mainstay treatment for combined variable immunodeficiency is based on the replacement of the deficient immunoglobulins with regular infusions, usually at a dose of 400–600 mg/kg body weight per month[2]. Our patient was initiated on periodic IVIG infusions after her preliminary diagnosis, however, she did not have a good clinical response evidenced by the persistent low levels of immunoglobulins (Figs 1 and 2), continued episodes of ear, occasional gastrointestinal disturbances, and upper respiratory infections that eventually lead to the development of bronchiectasis. But it is to be noted

that the patient did not suffer from any life threatening or serious infections during this period. A prospective cohort study focused on follow-up and outcomes of CVID patients post-IVIG transfusions stated that there is a significant reduction of acute infections but an increase in the prevalence of chronic diseases, which does not completely align with our findings as there is no significant reduction in acute infections, however, the development of bronchiectasis in our patient correlates with the findings of this study[16].

Considering the endocrine aspects of this case, the patient is suffering from a growth hormone deficiency and also a vitamin D deficiency, that was incidentally diagnosed. Usually, GHD is treated with recombinant human growth hormone (rhGH), given subcutaneously at a dose of 25–100 μg/kg/day. Our case was treated with a course of somatropin 600 μg daily, for which she showed an adequate response[25]. The standard treatment protocol for vitamin D deficiency by the Endocrine Society for children aged 1–18 years is 2000 IU/d of vitamin D_2 or vitamin D_3 for at least 6 weeks or with 50 000 IU of vitamin D_2 once a week for at least 6 weeks[26]. This patient was treated with 1500 IU D_2 for a period of 6 months and upon re-examination of laboratory values, the Vitamin D levels reached normal reference range, indicating successful treatment of the deficiency.

The already complex clinical scenario of diagnosing a primary immunodeficiency disorder coexisting with multiple endocrine disorders gets even more entangled when the patient needs to be put on a well-tailored treatment regimen that not only addresses the etiology and treats the acute exacerbations but also prevents chronic complications. The suboptimal response of this patient to the IVIG infusions is not completely understood but may also be due to the sophisticated interplay between various factors that were discussed earlier, increasing the need for comprehensive guidelines for the clinicians to follow in such situations.

Conclusion

In conclusion, the case underscores the intricate challenges individuals face when grappling with dual health conditions, like CVID coexisting with GHD, especially at such a young age. The patient's recurrent respiratory infections and the need for ongoing medications, including IVIG, GH therapy, vitamin D therapy, and antibiotics, highlight the multifaceted nature of the management of such cases. Despite the difficulties posed by living with CVID, the patient's prognosis appears promising with the current treatment plan, which includes a tailored regimen of IVIG and GH therapy. The identification of antipituitary antibodies, IGF1, and vitamin D as potential links between CVID and GHD adds a layer of complexity to the diagnostic workup needed for the cases like these. Consequently, many patients may not come to light due to the lack of cognizance and facilities at the level of the healthcare providers, and poor financial backup on the patient's end. It, therefore, highlights the need for meticulous diagnostic workup and a holistic treatment approach. We hope this case serves as a valuable contribution to the growing body of knowledge surrounding the coexistence of immunodeficiency and endocrine disorders.

Ethical approval

Ethical approval was not required for case report as per our university guidelines. Only consent from the patient is enough.

Consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Source of funding

No funding received.

Author contribution

M.S.K., M.S., and M.D.: conception or design of the work; M.S., M.D., A.N., P.C.G.M., and M.G.: first draft of the article; S.T.K., M.G., A.N., and P.C.G.M.: critical revision of the article; S.T.K. and M.G.: supervision of article; M.S.K. and M.G.: project administration. All authors contributed in final approval of the version to be published.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Majety SK and Muppana G.

Data availability statement

Not applicable.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Acknowledgements

Special thanks to Squad Medicine and Research (SMR) for their guidance and help in publication.

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