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Abstract

Common Variable Immunodeficiency (CVID) is the most common symptomatic Inborn Errors of Immunity in adults, characterized by hypogammaglobulinemia and impaired antibody responses. Despite its prevalence, limited clinical awareness frequently results in delayed diagnosis and preventable complications. We describe a case series of three adult patients identified shortly after a targeted educational workshop for family physicians in a low-awareness setting. All patients presented with recurrent respiratory tract infections as their initial clinical first major clinical manifestation. Complications included bronchiectasis, pleural empyema, chronic bronchitis, and, in one severe case, profound weight loss, chronic obstructive pulmonary disease, and cor pulmonale. Diagnostic delays ranged from 2 to 10 years. All patients demonstrated markedly reduced IgG, IgA, and/or IgM levels, meeting ESID diagnostic criteria. Immunoglobulin replacement therapy led to clinical stabilization and decreased infection burden. This series highlights the value of clinical education in improving CVID recognition and diagnostic delay.

Keywords: *Common variable immunodeficiency, CVID, Inborn Errors of Immunity, Adult, Diagnostic delay, Complications.*

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Резюме

УЛУЧШЕНИЕ ВЫЯВЛЯЕМОСТИ ОБЩЕЙ ВАРИАБЕЛЬНОЙ ИММУННОЙ НЕДОСТАТОЧНОСТИ С ДЕБЮТОМ ВО ВЗРОСЛОМ ВОЗРАСТЕ ПОСЛЕ ЦЕЛЕВОГО ОБРАЗОВАТЕЛЬНОГО СЕМИНАРА: СЕРИЯ КЛИНИЧЕСКИХ СЛУЧАЕВ ИЗ КАЗАХСТАНА

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Общая вариабельная иммунная недостаточность (ОВИН) является наиболее распространенной симптоматической формой врожденных ошибок иммунитета у взрослых и характеризуется гипогаммаглобулинемией и нарушением антительного ответа. Несмотря на ее распространенность, недостаточная клиническая осведомленность нередко приводит к поздней диагностике и развитию предотвратимых осложнений. В настоящем исследовании предоставлена серия клинических случаев трех взрослых пациентов, выявленных вскоре после проведения целевого образовательного семинара для врачей общей практики в условиях низкой осведомленности. У всех пациентов первичным клиническим проявлением были рецидивирующие инфекции дыхательных путей.

Осложнения включали бронхоэктазы, плевральную эмпиему, хронический бронхит и, в одном тяжелом случае, выраженную потерю массы тела, хроническую обструктивную болезнь легких и легочное сердце. Задержка в постановке диагноза составляла от 2 до 10 лет. У всех пациентов выявлены значительно сниженные уровни IgG, IgA и/или IgM, соответствующие диагностическим критериям Европейского общества по иммунодефицитам (ESID). Назначение заместительной терапии иммуноглобулинами привело к клинической стабилизации и снижению частоты инфекций. Представленная серия случаев подчеркивает значимость клинического образования для улучшения распознавания ОВИН и уменьшения диагностической задержки.

Ключевые слова: *Общий вариабельный иммунодефицит, ОВИД, врожденные нарушения иммунитета, взрослые, задержка диагностики, осложнения.*

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Түйіндеме

МАҚСАТТЫ БІЛІМ БЕРУ СЕМИНАРЫНАН КЕЙІН ЕРЕСЕК ЖАСТА БАСТАЛАТЫН ЖАЛПЫ ВАРИАБЕЛЬДІ ИММУНДЫҚ ЖЕТКІЛІКСІЗДІКТІ ДИАГНОСТИКАЛАУДЫҢ ЖАҚСАРУЫ: ҚАЗАҚСТАННАН КЛИНИКАЛЫҚ ЖАҒДАЙЛАР СЕРИЯСЫ

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Жалпы вариабельді иммундық тапшылық (ЖВИТ) - ересектерде гипогаммаглобулинемиямен және антидене реакцияларының бұзылуымен сипатталатын туа біткен иммунитет ақауларының ең көп таралған түрі. Таралуына қарамастан, клиникалық хабардарлықтың шектеулі болуы көбінесе диагноздың кешіктіріліп қоюына және алдын алуға болатын асқынуларға әкеледі. Біз отбасылық дәрігерлерге арналған мақсатты білім беру семинарынан кейін көп ұзамай үш ересек пациенттің жағдайлар сериясының анықталғанын сипаттаймыз. Барлық пациенттер негізгі клиникалық көрінісі ретінде қайталанатын тыныс алу жолдарының инфекцияларымен келгендігі анықталды. Асқынулары бронхоэктаз, плевра эмпиемасы, созылмалы бронхит және бір ауыр науқаста салмақтың күрт төмендеуі, созылмалы обструктивті өкпе ауруы және өкпелік жүрек түрінде көрінді. Диагностикалық кешігулер 2 жылдан 10 жылға дейін болды. Барлық пациенттерде IgG, IgA және/немесе IgM деңгейлерінің айтарлықтай төмендегені байқалды, бұл ESID диагностикалық критерийлеріне сәйкес келеді. Иммуноглобулинді алмастыру терапиясы клиникалық тұрақтандыруға және инфекция жүктемесінің төмендеуіне әкелді. Бұл жағдайлар ЖВИТ тануды және диагностикалық кешігуді болдырмаудағы клиникалық білім берудің маңыздылығын көрсетеді.

Түйінді сөздер: *Жалпы вариабельді иммундық тапшылық, ЖВИТ, туа біткен иммунитет ақауы, ересек, диагностикалық кешігу, асқынулары.*

Дәйексөз үшін:

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Introduction

Common Variable Immunodeficiency Disorder (CVID) is characterized by defective antibody production, presenting clinically as recurrent sinopulmonary infections, autoimmune complications, granulomatous diseases, enteropathy, and an increased risk of malignancy. The

estimated prevalence varies between 1:25,000 and 1:50,000 worldwide [1, 2]. While the onset can occur at any age, a bimodal distribution is often observed, with a significant peak in adulthood (ages 20 and 40).

The hallmark of CVID management is early diagnosis to prevent structural lung damage (e.g., bronchiectasis) and associated morbidity. However, diagnostic delay remains a global challenge. The European Society for Immunodeficiencies (ESID) Registry indicate a mean delay of 8.8 years between onset and diagnosis. In developing healthcare systems, this delay is often longer due to limited immunological testing capabilities and low awareness among general practitioners [4].

To address this gap, a grant-funded educational initiative was launched in the southern region of Kazakhstan. A targeted educational workshop was conducted for family physicians (General practitioners), focusing on the clinical warning signs of IEIs, ESID diagnostic criteria, and referral pathways. This study reports on the first three adult CVID patients diagnosed in our center, all of whom were referred by workshop attendees shortly after the training, illustrating the direct translational impact of medical education on case detection.

Case description

All patients provided informed consent for the publication of their clinical data. The diagnosis of CVID was established based on the ESID criteria: marked decrease in IgG combined with reduced IgA and/or IgM, and exclusion of secondary causes of hypogammaglobulinemia.

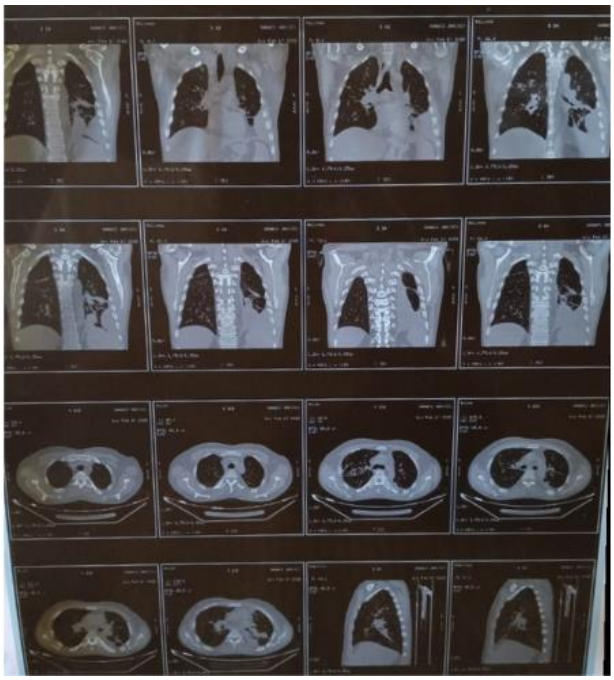
Patient 1. The "Chronic obstructive pulmonary disease (COPD)" mimic.

A 45-year-old male was referred in April 2025 with a history of recurrent respiratory tract infections, productive cough, and dyspnea (mMRC grade 2). His history included a documented pneumonia in May 2023, followed by 3-4 episodes in 2024 and another in January 2025. In early 2025, he was hospitalized in a pulmonary department in Almaty with diagnoses of left-sided loculated pleural effusion, pnemofibrosis, and COPD (Category B). He also had Type 2 diabetes mellitus.

Physical examination revealed a scattered wheezing. High-resolution chest Computed Tomography demonstrated bilateral post-inflammatory fibrosis, right-sided bronchiectasis, and signs of chronic bronchitis (Figure 1a, b). Immunological testing on March 3, 2025, confirmed profound hypogammaglobulinemia: IgG 0.7 g/L (reference: 7.0–16.0), IgA 0.6 g/L (reference 0.7–4.0), and IgM 1.08 g/L (reference 0.4–2.3). Secondary causes, including protein-losing enteropathy and lymphoproliferative malignancies, were excluded. The patient was commenced on immunoglobulin replacement therapy (IgRT).

a.

(a) Coronal Reconstructions: HRCT images demonstrating extensive post-inflammatory fibrosis (arrows) and architectural distortion in the lung parenchyma.



b.

(b) Axial View: HRCT image confirming the presence of cylindrical and traction bronchiectasis (starred areas) in the right lower lobe.

Figure 1. High-resolution Computed Tomography (HRCT) of the chest, Patient 1.

Patient 2. The decades-long diagnostic delay.

A 33-year-old male presented with a 4-month history of persistent cough, recent fever (39°C), and exertional dyspnea. He reported 3–4 episodes of pneumonia annual since the age of 20. Bronchiectasis had been diagnosed a decade prior (2015), yet no immunological workup was performed at that time.

Following the educational workshop, his primary care physician suspected IEI and referred him for evaluation. CT imaging revealed a “tree-in-bud” pattern, bilateral polysegmental pneumonia, and extensive bronchiectasis, particularly in the lower lobes (Figure 2). Immunological evaluation on January 2024 and 2025, revealed: IgA 0.11 g/L (reference: 0.7–4.0), IgG 0.67 g/L (7.0–16.0), and IgM

0.49 g/L (0.4–2.3). The patient had no history of systemic steroids or immunosuppressive drug use. The diagnosis of CVID was confirmed, ending a diagnostic delay of 13 years.

Patient 3. CVID enteropathy and severe sepsis.

A 21-year-old man presented in severe condition with fever, cachexia (weight loss of 7 kg over 2 months), and respiratory failure. His medical history was complex: he was diagnosed with celiac disease in 2015, and had suffered recurrent pneumonia since 2019. He had multiple prior hospitalizations for "severe COPD" and bronchiectasis.

On admissions in May 2025, he was cachetic (Weight 35 kg, Height: 1.38 m) with digital clubbing ("drumstick" fingers) and central cianosis (SpO2-70% on room air). Laboratory investigations revealed critical pan-hypogammaglobulinemia: IgA – 0.01 g/l (reference: 0.7–4.0), IgG – 0.15 g/l (reference: 7.0–16.0), IgM - 0.07 g/l (reference: 0.4–2.3), inflammatory markers were elevated (CRP - 208.4 mg/l (reference: 0-5)), and sputum culture was positive for Streptococcus pneumoniae (Table 1). Secondary protein loss via the kidneys was excluded (normal urinalysis). While the patient carried diagnosis of celiac disease, the severity of the IEI suggests this may represent CVID-associated enteropathy, a known phenotype of the disorder. He was immediately started in IVIG and broad-spectrum antibiotics.

A detailed summary comparing the demographic information, immunological profiles, diagnostic delays, and clinical complications for all three patients is provided in Tables 2 and 3.

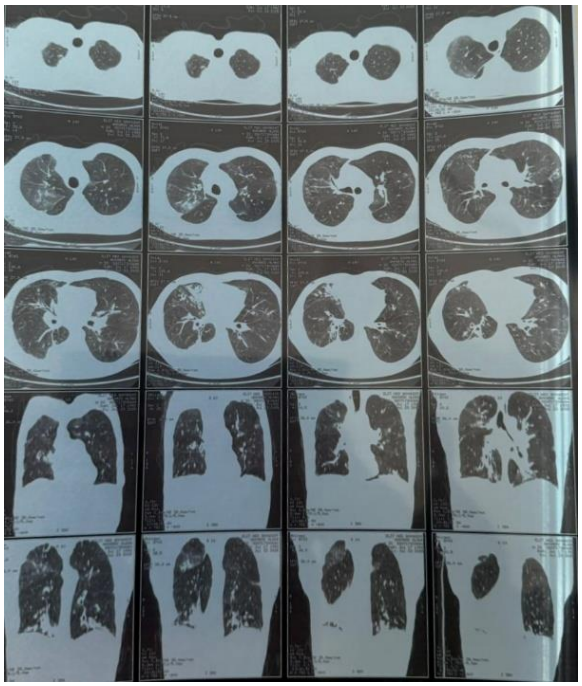


Figure 2. High-resolution Computed Tomography (HRCT) of the chest, Patient 2.

**** HRCT images demonstrating diffuse evidence of bronchiolitis, characterized by the "tree-in-bud" sign (small centrilobular nodular opacities with linear branching). Multiple lung segments exhibit established extensive cylindrical bronchiectasis, predominantly in the lower and mid-lung zones.***

Table 1.

Results of sputum culture and antimicrobial sensitivity profile (Patient 3).

Microorganism isolated	Antimicrobial agent	Sensitivity (S)/Resistance (R)
Streptococcus pneumoniae	Ceftazidime	S
	Cefepime	S
	Gentamicin	S
	Cefoperazone	S
	Ceftriaxone	S

**culture was performed on sputum sample collected upon admission on 14 May 2025. The organism showed pan-sensitivity to the tested cephalosporins.*

Table 2.

Comparative clinical and immunological characteristics of the diagnosed patients.

Characteristic	Patient 1	Patient 2	Patient 3
Demographics (Age/Sex)	45/Male	33/Male	21/Male
Age at Symptom Onset (years)	43	20	11 (Enteropathy)
Age at diagnosis (years)	45	33	21
Diagnostic delay (years)	2	13	10
Infectious manifestations	Recurrent pneumonia, pleural effusion	Recurrent pneumonia (3-4 years), "tree-in-bud" sign	Recurrent pneumonia
Structural lung damage	Pneumofibrosis, bronchiectasis	Extensive bilateral bronchiectasis	Severe bronchiectasis, cor pulmonale
Autoimmunity/Enteropathy	No	No	Celiac-like enteropathy, malabsorption
Referred following educational workshop?	Yes	Yes	Yes

Table 3.

Key laboratory parameters at diagnosis for all patients.

Test name	03/2025	01/2025	05/2025	Reference range	Unit

IgG serum	0.70	0.67	0.15	7.0-16.0	g/L
IgA serum	0.60	0.11	0.01	0.7-4.0	g/L
IgM serum	1.08	0.49	0.07	0.4-2.3	g/L
CRP	-	-	208.4	0-5	Mg/L

Discussion

The case series reports the first adult patients diagnosed with CVID in our clinical practice all identified as a direct result of a targeted educational workshop for family physicians. The study highlights two critical issues in the management of IEI: the heterogeneity of the disease and the effectiveness of educational interventions in settings with low awareness.

All three patients fulfilled the ESID diagnostic criteria for probable CVID. Key features included a marked reduction in IgG (all < 1.0 g/L in this cohort) and reduced IgA/IgM, alongside a clinical phenotype of reccurent bacterial infections [3]. In our patients, secondary causes of hypogammaglobulinemia – such as drug-induced suppression (e.g., steroids, rituximab), lymphoproliferative disorders, and severe protein-losing states – were clinically ruled out. Note: while vaccine response testing is often used to confirm impaired antibody production, the severity of hypogammaglobulinemia in these patients (IgG < 3.0 g/L) and the urgency of treatment necessitated the immediate initiation of IgRT, supporting the diagnosis based on baseline levels and clinical history alone.

The cases illustrate the progressive nature of undiagnosed CVID. Patient 2 experienced a diagnostic delay over a decade, resulting in established bronchiectasis. Patient 3 represents a severe "enteropathic" phenotype. Although previously diagnosed with celiac disease, his profound weight loss and malabsorption are likely manifestations of CVID enteropathy. Distinguishing between classical celiac disease and CVID-associated villous atrophy is challenging but vital, as CVID patients do not always respond to a gluten-free diet alone and require aggressive IgRT [5].

The most significant finding of this series is the mechanism of ascertainment. In Kazakhstan, recurrent pneumonia is typically managed by pulmonologists who may focus on structural damage (COPD, bronchiectasis) rather than underlying etiology. By training primary care providers to recognize "warning signs" – such as bronchiectasis without smoking history or recurrent infections in young adults – we successfully bridged the gap between primary care and specialized immunology services.

Conclusions

Early detection and timely initiation of immunoglobulin replacement therapy are essential to prevent irreversible organ damage in CVID. This series demonstrates that targeted education of family physicians is a highly effective, low-cost intervention to improve case detection in regions where adult IEIs are underrecognized.

Declarations

Disclaimer

This section states any applicable disclaimers.

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Author contributions

G.Z.: Conceptualization, Funding acquisition, Investigation, Methodology, Writing - original draft, Writing - review & editing. A.A.: Conceptualization, Methodology, Visualization, Writing - original draft, Writing - review & editing. B.K.: Conceptualization, Data curation, Methodology, Writing - original draft. Z.M.: Conceptualization, Data curation, Methodology, Writing - original draft. A.O.: Conceptualization, Funding acquisition, Investigation. K.B.: Conceptualization, Data curation, Investigation.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

The study was approved by the Institutional Ethics Committee of Khoja Akhmet Yassawi International Kazakh-Turkish University Approval No. 121, Date: 02/09/2025.

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Informed consent to publication was obtained from relevant participants.

Availability of data and materials

All data underlying the results of this case series are fully contained within the published article and accompanying tables. No additional source data are required.

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Abbreviations

CT: Computed tomography
CVID: Common Variable Immunodeficiency
ESID: European Society for Immunodeficiencies
IgRT: Immunoglobulin replacement therapy
IVIG: Intravenous immunoglobulin G
SCIG: Subcutaneous immunoglobulin G

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