# An Unusual Case of Agammaglobulinemia

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Agammaglobulinemia was the first primary immunodeficiency identified in humans. It is characterized by an absent or significantly reduced number of mature B cells, decreased serum immunoglobulins, and recurrent infections beginning in infancy. The entity was first described in 1952 by Colonel Ogden Bruton at the Walter Reed Army Hospital in the United States. Bruton reported on an 8-year-old boy who had experienced 19 episodes of pneumonia over 4 years and was found to have a complete absence of antibody-containing γ-globulins in his serum [1].

Over time, through improvement in the immune and genetic investigations, our understanding of agammaglobulinemia has expanded enabling earlier diagnosis and treatment resulting in a change of the disease course.

## PATIENT DESCRIPTION

A 15-year-old female presented with recurrent infections since the age of 8 months. She was born at term following a normal pregnancy and delivery. Since the age of 8 months, she experienced recurrent purulent otitis media necessitating tympanostomy tube placement at the age of 9 months. At 10 months she presented with two episodes of pneumonia in different lobar locations. In addition, she presented with chronic diarrhea, and failure to thrive starting at 6 months of age. Bronchiectasis was diagnosed at age 4 years by chest computed tomography. At the age of 11 years she was diagnosed with asthma.

A bilateral hearing impairment was noted from birth. An investigation for congenital cytomegalovirus infection was inconclusive and therefore she was treated with valganciclovir for over a year. At the age of 2 years she underwent cochlear implantation due to delayed language development. The patient is the first-born child of non-consanguineous parents. The mother is of Persian descent, and the father is of Egyptian and British descent. Both parents are healthy and there is no known history of hereditary diseases among family members.

Immunological workup at the age of 11 months revealed agammaglobulinemia with normal absolute counts of T and B cells, absent memory B cells (CD20+CD27+) with normal T-cell proliferative responses to mitogens [Table 1].

Due to the clinical presentation of recurrent respiratory infections and agammaglobulinemia, a diagnosis was made and a monthly immunoglobulin replacement therapy was initiated.

In terms of genetic diagnosis, chromosomal microarray (CMA) was initially performed revealing a terminal deletion on the long arm of chromosome 4, measuring 5.755 Mb (185,399,431–191,154,276, hg19). The region includes seven morbid OMIM genes: SLC25A4, UFSP2, TLR3, F11, CYP4V2, KLKB1, and PRIMPOL, none of which is associated with agammaglobulinemia or B-cell abnormalities. Patients with similar deletions have been reported to have sensorineural hearing loss and neurodevelopmental disorders, but none was reported with immunodeficiency. Therefore, an immunodeficiency gene panel was performed (Invitae Primary Immunodeficiency Panel of 407 genes, Labcorp, USA), which did not identify relevant pathogenic variants. Whole exome sequencing is scheduled for further genetic analysis.

She currently continues treatment with immunoglobulin replacement therapy, inhaled corticosteroid/long-acting β2 agonist combination inhaler, and pulmonary physiotherapy.

## COMMENT

We reported on a female patient who presented at a young age with recurrent sinopulmonary infections, sensorineural hearing loss, asthma, and bronchiectasis. An immunologic evaluation demonstrated agammaglobulinemia with normal B-cell

counts and reduced class-switched memory B cells. Genetic analysis did not reveal specific gene variants known to cause immunodeficiency.

Agammaglobulinemia is characterized by absent or markedly reduced immunoglobulin production and typically results from defects in B-cell development leading to primary B-cell immunodeficiency. In contrast, hypogammaglobulinemia refers to decreased, but still detectable, immunoglobulin concentrations and encompasses a broader spectrum of primary and secondary disorders. Agammaglobulinemia may be primary, due to inborn error of immunity (IEI) or secondary to other disease processes. Primary agammaglobulinemia usually presents with recurrent infections before 5 years of age. Laboratory investigations typically reveal < 2% of circulating B cells and significantly reduced serum IgG levels, reflecting a B-cell maturation defect.

The most common cause of primary agammaglobulinemia is X-linked agammaglobulinemia (XLA) accounting for approximately 85% of cases. XLA is caused by mutations in the Bruton tyrosine kinase (BTK) gene, which is essential for B-cell development and B-cell receptor signaling [1]. Additional autosomal recessive and dominant negative XLA phenocopies have been reported due to variants in IGHM (Igμ chain), IGLL1 (λ5 surrogate L chain), CD79A (Igα), CD79B (Igβ), BLNK, PIK3R1, or PIK3CD genes all of which are involved in B-cell development and receptor signaling. Other genetic causes associated with near absence of mature B-cells include variants in TCF3, SPI1, SLC39A7, FNIP1, PAX5, LRRC8A, and TOP2B, which play a role in early B-cell development. In some patients no genetic etiology is identified [2].

**Table 1.** Immune evaluation of our patient

| Parameter | Results | | Normal range / control |
|---|---|---|---|
| White blood cell count | 9500 | | 5000–15000 |
| Absolute neutrophil count | 900 | | > 1500 |
| Absolute lymphocytes count | 6400 | | > 2000 |
| Absolute eosinophils count | 200 | | 0–500 |
| **Immunoglobulins** | | | |
| IgA mg/dl | < 6 | | 14–91 |
| IgM mg/dl | < 4 | | 33–150 |
| IgG mg/dl | 26 | | 348–941 |
| **PMN proliferation response to mitogens** | | | |
| **No mitogen** | 866 | | 1045 |
| **PHA 6 µg/ml** | 51,267 | | 63,500 |
| **PHA 25 µg/ml** | 25,498 | | 29,863 |
| **CD3 Mitogen** | 28,675 | | 19,964 |
| **Lymphocyte immunophenotyping (cells/mm³)** | **Age 13 months** | **Age 5 year** | |
| **WBC** | 17,680 | 11,360 | |
| **Lymphocytes** | 7249 | 3181 | |
| **CD3 (mature T)** | 3914 (54%) | 2290 (72%) | 60–85% |
| **CD4** | 2610 | 1495 | 436–1394 |
| **CD8** | 1232 | 859 | 166–882 |
| **CD4/CD8 ratio** | 2.12 | 1.74 | 1.5–3.3 |
| **CD20 (mature B)** | 2755 (38%) | 573 (18%) | 100–300 (5–25%) |
| **CD40+CD20+** | 35% | 96% | |
| **CD20+CD27+** | 0 | 11% | |
| **CD20+CD38+** | 38% | 14% | |
| **CD19+ IgM+IgD+** | | 90% | |

PMN = polymorphonuclear neutrophils, WBC = white blood cells

Agammaglobulinemia with a normal B cell count points to a defect downstream of B cell generation, such as impaired terminal differentiation, or class-switch recombination or B-cell survival, rather than a block in B cell development itself. Reported genetic causes include *CD40LG*, *CD40*, *AICDA*, and *UNG* defects, as well as OBF-1 (*POU2AF1*) deficiency, in which agammaglobulinemia and absent class-switched memory B cells occur despite a normal peripheral B cell count [3].

Secondary agammaglobulinemia may develop as a result of malignancy, particularly chronic lymphocytic leukemia and multiple myeloma, gastrointestinal protein loss, or renal protein loss (nephrotic syndrome). In addition, immunosuppressive medication can cause agammaglobulinemia, most notably B-cell-targeted therapy [4].

Patients with agammaglobulinemia will often present with respiratory infections, particularly pneumonia, which are the leading cause of morbidity and mortality. Other frequent infections are recurrent oti-

tis media, sinopulmonary infections, diarrhea, conjunctivitis, and skin infections. Approximately 60% of affected individuals are diagnosed with immunodeficiency following severe, life-threatening infections such as pneumonia, empyema, meningitis, or sepsis [1]. The common pathogens include *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Giardia lamblia* [2]. Viral infections are generally not more severe, although chronic or severe enteroviral meningoencephalitis is a recognized risk, particularly in XLA.

Historically, 5–10% of individuals with XLA developed vaccine-associated poliomyelitis following administration of live attenuated oral polio vaccine [1]. Non-infectious manifestations of primary agammaglobulinemia include inflammatory and autoimmune manifestations such as inflammatory bowel disease and arthritis [2]. Malignancies are uncommon in XLA and primarily involve the gastrointestinal tract, the thyroid gland, and the central nervous system [4].

Other causes of significantly reduced levels of immunoglobulins are primary immunodeficiency such as common variable immunodeficiency. In these cases, B-cell counts are typically normal or near normal, with impaired switch to memory B-cells. Clinical presentation usually occurs later than in agammaglobulinemia, most often after 5 years of age. Reduced levels of immunoglobulins in the setting of low T cells numbers suggest of combined immunodeficiency of various genetic causes [1].

Whole-exome sequencing (WES) and gene panels have become an essential tool in diagnosing IEIs, with reported diagnostic yields of approximately 25–45%, particularly in patients with severe, syndromic, or familial phenotypes.

Management of agammaglobulinemia consists of life-long immunoglobulin (Ig) replacement therapy. Early initiation Ig replacement therapy and maintaining therapeutic IgG levels effectively reduce infection rates, morbidity, and mortality [1]. Prophylactic antibiotics may prevent infection frequency and decrease the risk of chronic sinusitis and lung disease. Vaccinations, excluding live vaccines, are recommended to prevent infection [1]. Emerging gene-based therapies are currently being investigated.

Most individuals with agammaglobulinemia live a normal life. Nevertheless, approximately 10% experience significant infections despite appropriate therapy, and many develop chronic pulmonary disease [1]. In an XLA cohort, the overall survival rate at 43 years of age was 92.7%, which is significantly lower than the rate for age-matched healthy controls (98%) [5]. Bronchiectasis and chronic lung disease are complications that may progress to requiring lung transplantation [2]. Prognosis has improved markedly in the last 25 years due to earlier diagnosis, improved immunoglobulin preparations allowing normalization of serum IgG levels, and more liberal use of antibiotics. However lifelong monitoring is essential [1].

The impact of earlier diagnosis on infection-related morbidity and mortality in XLA has prompted initiatives to include B-cell defect screening in newborn screening. Screening for Kappa-deleting element recombination circles (KRECs), which are byproducts of B-cell maturation, enables early detection of XLA and autosomal recessive agammaglobulinemia [2]. Newborn screening for B-cell disorders is scheduled to be implemented in Israel during 2026.

## CONCLUSIONS

We reported on a 15-year-old girl who presented with recurrent infections beginning at 8 months of age. Immunologic evaluation revealed near-absent immunoglobulins in the presence of a normal number of circulating B cells and absent memory B cells, with no identifiable genetic etiology. This case elucidates the broad spectrum of IEI that disrupt B-cell function and highlights the complexity of humoral immunity beyond classical BTK-associated Agammaglobulinemia. A review of the literature, derived mainly from studies on BTK agammaglobulinemia, underscores the need for further studies to expand our understanding of the human B-cell development and differentiation and their impact on humoral immunity.

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