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Volume 2

PATHOLOGY OF IMMUNOGLOBULINS:
Diagnostic and Clinical Aspects

Stephan E. Ritzmann, Editor

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Protein Abnormalities, Volume 2

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DIAGNOSTIC AND CLINICAL ASPECTS

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Protein Abnormalities

Volume 1
Physiology of Immunoglobulins: Diagnostic and Clinical Aspects
Stephan E. Ritzmann, *Editor*

Volume 2
Pathology of Immunoglobulins: Diagnostic and Clinical Aspects
Stephan E. Ritzmann, *Editor*

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Preface

The history of many classic biological disciplines has shown periods of extraordinary ferment accompanied by logarithmic increases in verifiable knowledge. A decade ago it became evident that biochemistry, cell physiology, genetics, endocrinology, and immunology were in such a garguantuan growth phase. Clinical and laboratory proteinology is emerging now as a functional discipline in its own right. It has provided insight into the biological roles of numerous proteins, such as the immunoglobulins, complement, oncofetal proteins, carrier proteins, and protease inhibitors. Together with immunological approaches, it has produced the modern diagnostic tools that aid in the detection and characterization of numerous proteins and their clinical effects. Many of the major advances of the past 10 years are presently in clinical use for the benefit of the patient, and many more are potentially applicable. This progress reflects the state of flux of a growing field.

In a series of books on protein abnormalities the multifaceted spectrum of proteinology will be presented by experts in basic, laboratory, and clinical fields. Volumes 1 and 2 deal with the physiologic, pathologic, diagnostic, and clinical aspects of the immunoglobulins. The monoclonal gammopathies—in particular, their usual and unusual manifestations, amyloidosis, hyperviscosity, and Bence Jones proteins—are extensively considered in this volume. These major immunoglobulin abnormalities are experiments of nature that have profound implications for both the healthy and the sick.

The increasing awareness of nutritional deficiencies and the affliction by parasitic infections of hundreds of millions of individuals worldwide have necessitated the inclusion of these subjects in later volumes. Likewise, the growing need for solid, basic information supportive of the diagnosis and treatment of pediatric and geriatric diseases warrants their special consideration. Further, the ever-increasing need for clinically relevant information concerning the amino acids and peptides and, in particular, their abnormalities in newborns has necessitated the addition of these relatively new topics.

This series reflects a concerted effort to present updated material in emerging areas of importance, without necessarily superseding the information presented in the earlier book *Serum Protein Abnormalities: Diagnostic and Clinical Aspects* [1]. These volumes are intended to provide the personnel involved in health care delivery with a distillation of current information on serum proteins and their counterparts in other

biological fluids, as well as their relation to clinical and immunological aspects, in a practical and selective, rather than encyclopedic, fashion. The textual material is supplemented generously with illustrations and tables.

Foremost among the potential audience of this series are the clinician, clinical pathologist, clinical chemist, medical technologist, and other laboratory personnel, but a broader audience—medical students, house officers, practicing physicians, and educators—may find in it a spectrum of useful information. Emphasis has been placed on the complex relationship between human disease and protein pathophysiology, as it relates to diagnosis, therapy, and prevention. It is hoped that this attempt at bridging the widening gap between "bench" and "bed" will provide for the busy professional charged with the responsibility for patient care a valuable addition to his armamentarium and a reliable companion in times of need.

1. Ritzmann SE, Daniels JC: "Serum Protein Abnormalities: Diagnostic and Clinical Aspects," 2nd printing. New York: Alan R. Liss, Inc., 1982.

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Introduction

Stephan E. Ritzmann, MD

The recognition of hypo-γ-globulinemia and its association with increased susceptibility to infections in a patient with chronic lymphocytic leukemia by Löffler in 1951 [1] and the demonstration of salutory effects of γ-globulin substitution therapy in a child with congenital A-γ-globulinemia by Bruton in 1952 [2,33] clearly presented the clinical need for practical quantitative and qualitative diagnostic assays for immunoglobulins (Igs) and their abnormalities. The introduction of radial immunodiffusion (RID) in 1965 by Mancini et al. [3] and Fahey and McKelvey [4] provided such a basic quantitative laboratory tool [6,9a,9b], which revolutionized the entire area of diagnostic protein quantitation in the clinical laboratory. Subsequently, other quantitative techniques, such as quantitative immunoelectrophoresis, nephelometry, and turbidimetry [10,16,21,28–31,34,36,43,46–49,53,64,65], have been introduced which were supplemented by powerful qualitative routine assays, mainly immunoelectrophoresis (IEP) [7,8,10,16–19,23,36,38–40, 43,48–50,52,61,62,68].

The term *γ-globulin* was initially equated with those proteins possessing antibody characteristics. The application of IEP has resulted in the demonstration of the electrophoretic distribution of antibody proteins within the entire γ-, β- and α_2-globulin ranges. Consequently, the functional and all-encompassing term *immunoglobulin* has been introduced by Hitzig [69] and Heremans [23] for those proteins possessing either antibody characteristics or the characteristic structure of antibodies. Quantum leaps of knowledge acquisition regarding Ig synthesis, regulation, structure, functions, and metabolism have subsequently occurred [5,8,10,16,20,27,32,35,40,53–58].

Immunoglobulin abnormalities are conventionally classified into three categories: *hypo-γ-globulinemias, polyclonal gammopathies,* and *monoclonal gammopathies*. These abnormalities are reflected by characteristic changes of serum protein electrophoresis (SPE) patterns [8].

HYPO-γ-GLOBULINEMIAS

Hypo-γ-globulinemias may be associated with a wide range of disorders of varied etiology (Table I). Decreases in the electrophoretic γ-globulin fraction and the IgG, A, M contained therein can result from either *decreased Ig synthesis, increased loss, hypercatabolism* or a *combination* of these factors [5a,5b,8,10,63].

Decreased Ig Synthesis

Primary Ig immunodeficiencies resulting from decreased Ig synthesis are most frequently detected during childhood. These include combined B/T-cell immunodeficiencies, sex-linked A-γ-globulinemia, selective IgA, IgM, κ- or λ-light (L) chain deficiencies, IgG subclass deficiencies, and others [8,10–13,32,33,35,63,66,67]. The mechanisms leading to these Ig deficiencies are diverse and incompletely understood. Defective B-cell differentiation appears to be the culprit in many of these patients.

Secondary Ig deficiencies due to decreased synthesis are principally encountered in adult patients. The majority of these Ig deficiencies cannot be unequivocally classified, and such disorders are therefore grouped under the heading "common, variable, unclassifiable hypo-γ-globulinemias" [5a,5b, 10,63]. Well-known causes of secondary hypo-γ-globulinemia include chronic lymphocytic leukemia and treatment with immunosuppressive agents, as well as severe protein malnutrition.

TABLE I. Partial List of Diseases Associated With Decreased Serum Immunoglobulin Levels

Diseases	IgG	IgA	IgM
Decreased synthesis			
Severe combined immunodeficiency	↓ ↓↔↓ ↓ ↓	↓ ↓↔↓ ↓ ↓	↓ ↓↔↓ ↓ ↓
Sex-linked A-γ-globulinemia	↓ ↓↔↓ ↓ ↓	↓ ↓↔↓ ↓ ↓	↓ ↓↔↓ ↓ ↓
Common variable hypo-γ-globulinemias	↓↔↓ ↓ ↓	↓↔↓ ↓ ↓	↓↔↓ ↓ ↓
Selective IgA deficiency	N	↓ ↓ ↓	N
Selective IgM deficiency	N	N	↓ ↓ ↓
Immunosuppressive therapy	N↔↓ ↓	N↔↓ ↓	N↔↓ ↓
Severe malnutrition	N↔↓ ↓	N↔↓	N↔↓
Increased loss			
Nephrotic syndrome	N↔↓ ↓ ↓	N↔↓ ↓	N
Protein-losing gastroenteropathies	N↔↓ ↓ ↓	N↔↓ ↓ ↓	N↔↓ ↓ ↓
Acute thermal burns	↓↔↓ ↓ ↓	↓↔↓ ↓ ↓	↓↔↓ ↓ ↓
Hypercatabolism			
Hyperthyroidism	↓↔↓ ↓	↓↔↓ ↓	↓↔↓ ↓
Myotonic dystrophy	↓↔↓ ↓ ↓	N	N
Antibodies to immunoglobulins	↓↔↓ ↓	↓↔↓ ↓	↓↔↓ ↓

N = Normal, ↓ = slight decrease, ↓ ↓ = moderate decrease, ↓ ↓ ↓ = marked decrease, ↔ = range.

Increased Ig Loss

Excessive Ig losses occur most commonly through the kidneys (nephrotic syndrome), the gastrointestinal tract (protein-losing gastroenteropathies), and the skin (acute thermal burns) [8]. Renal protein loss is characterized by a disproportionate decrease of low molecular weight serum proteins (e.g., albumin) but retention of large molecular weight proteins (e.g., IgM) and varying degrees of IgG decreases. In contrast, wastage of serum proteins into the gastrointestinal tract or through the skin results in "bulk" loss of all proteins irrespective of their molecular weight, with resultant deficiency of IgG, A, and M (and lymphocytes) [8,42].

Hypercatabolism of Ig

Hypermetabolic states occur in association with several disorders that result in decreased serum levels of one or more of the Ig classes. These conditions include hyperthyroidism, which can affect the levels of all Igs; myotonic dystrophy, which may be complicated by decreased levels of IgG due to its shortened half-life; and anti-Ig antibodies, which can affect any Ig class.

Serum concentrations of the five classes of immunoglobulins, G, A, M, D, and E, are age-dependent [5a,5b,8,10,32,33,35], and, therefore, their values in pediatric patients require reporting in age-adjusted terms. The *characterization of Ig deficiencies* is essential for etiologic, diagnostic, and therapeutic reasons.[1] For instance, the demonstration of a serum IgG concentration of 500 mg/dL in an adult patient mandates a search for the underlying etiology. On the other hand, an IgG level of < 100 mg/dL in such a patient may additionally necessitate γ-globulin substitution therapy to combat increased susceptibility to infections [5a,5b,8,20,22,63]. In general, adult serum IgG levels of < 200 mg/dL—i.e., less than one-fifth of the normal mean adult concentration—are often associated with an infectious diathesis.

HYPER-γ-GLOBULINEMIAS

Hyper-γ-globulinemias consist of essentially two varieties: the polyclonal and monoclonal gammopathies. These two categories can usually be distinguished by SPE analysis [8,21,39,40,43]. Unusual patterns of hyper-γ-globulinemia on SPE are often associated with circulating immune complexes [27,41].

Polyclonal Gammopathies (PG)

Hyper-γ-globulinemia of the polyclonal variety is generally characterized by a broad, diffuse, and heterogeneous increase mainly of the electrophoretic

[1]Ed. note: See also Chapter 7.

TABLE II. Partial List of Diseases Associated With Increased Serum Immunoglobulin Levels

Diseases	IgG	IgA	IgM
POLYCLONAL GAMMOPATHIES (PG)			
Infections	↑↔↑ ↑	N↔↑	↑↔↑ ↑
Infectious mononucleosis			
Subacute bacterial endocarditis	↑↔↑ ↑	↓↔N	↑↔↑ ↑
Tuberculosis	↑↔↑ ↑	N↔↑ ↑ ↑	↓↔N
Actinomycosis	↑ ↑ ↑	↑ ↑	↑ ↑ ↑
Deep fungus diseases	N	N↔↑	N
Bartonellosis	↑	↓↔N	↑ ↑↔↑ ↑ ↑
Trypanosomiasis	N↔↑	N↔↑	↑ ↑↔↑ ↑ ↑
Liver diseases			
Infectious hepatitis (late stage)	↑↔↑ ↑	N↔↑	N↔↑ ↑
Laennec's cirrhosis	↑↔↑ ↑ ↑	↑↔↑ ↑ ↑	N↔↑ ↑
Biliary cirrhosis	N	N	↑↔↑ ↑
Autoimmune disorders			
Lupus erythematosus	↑↔↑ ↑	N↔↑	N↔↑ ↑
Rheumatoid arthritis	N↔↑ ↑ ↑	↑↔↑ ↑ ↑	N↔↑ ↑
Sjögren's syndrome	N↔↑	N↔↑	N↔↑ ↑
Scleroderma	N↔↑	N	N↔↑
Miscellaneous			
Sarcoidosis	N↔↑ ↑	N↔↑ ↑	N↔↑
Hodgkin's disease	↓↔↑ ↑	↓↔↑	↓↔↑ ↑
Monocytic leukemia	N↔↑	N↔↑	N↔↑ ↑
Cystic fibrosis	↑↔↑ ↑	↑↔↑ ↑	N↔↑ ↑
Gluten-sensitive enteropathies	N	N↔↑ ↑ ↑	N
Berger's disease (IgA nephropathy)	N↔↑	↑↔↑ ↑ ↑	N↔↑
Henoch-Schoenlein syndrome	N↔↑	↑↔↑ ↑ ↑	N↔↑
MONOCLONAL GAMMOPATHIES (MG)			
IgG-MG (myeloma or asymptomatic form)	N↔↑ ↑ ↑	N↔↓ ↓ ↓	N↔↓ ↓ ↓
IgA-MG (myeloma or asymptomatic form)	N↔↓ ↓ ↓	N↔↑ ↑ ↑	N↔↓ ↓ ↓
IgM-MG (macroglobulinemia or asymptomatic form)	N↔↓ ↓ ↓	N↔↓ ↓ ↓	N↔↑ ↑ ↑
L chain disease (Bence-Jones myeloma)	N↔↓ ↓ ↓	N↔↓ ↓ ↓	N↔↓ ↓ ↓
IgD-MG (IgD ↑↔↑ ↑ ↑)	N↔↓ ↓ ↓	N↔↓ ↓ ↓	N↔↓ ↓ ↓
IgE-MG (IgE ↑↔↑ ↑ ↑)	N↔↓ ↓ ↓	N↔↓ ↓ ↓	N↔↓ ↓ ↓
Heavy chain diseases (HCD)			
γ-HCD	N↔↑ ↑ ↑	N↔↓ ↓ ↓	N↔↓ ↓ ↓
α-HCD	N↔↓ ↓ ↓	N↔↑ ↑ ↑	N↔↓ ↓ ↓
μ-HCD	N↔↓ ↓ ↓	N↔↓ ↓ ↓	N↔↑ ↑ ↑
(Chronic lymphocytic leukemia	N↔↓ ↓ ↓	N↔↓ ↓ ↓	N↔↓ ↓ ↓)

N = normal, ↑ = slight increase, ↑ ↑ = moderate increase, ↑ ↑ ↑ = marked increase, ↔ = range.

γ-globulin fraction, as a result of increased proliferation of numerous plasma cell clones. Usually all major Ig classes are increased with their normal κ/λ ratios preserved. Occasionally the Ig concentrations may reach extreme levels (e.g., IgG = 6.0–10.0 g/dL). *PG is, after hypoalbuminemia, the most frequently encountered serum protein abnormality, as detected by SPE.* No pathognomonic, diagnostic pattern can be obtained from the SPE pattern or the quantitation of these elevated Igs in individual patients, although on a statistical basis, such changes may be of diagnostic and clinical value. Nevertheless, monitoring of these Igs often provides useful and sometimes essential parameters in the therapeutic and prognostic follow-up of certain patients with PG. The spectrum of diseases associated with a PG is extremely varied; it includes numerous subacute and chronic infections, chronic liver diseases, autoimmune disorders, and others (Table II). It should be noted, however, that these Ig profiles in the various disorders may be secondary rather than primary in nature. For instance, sarcoidosis associated with PG may be a reflection of hepatic involvement by this disease, whereas sarcoidosis without liver affection may not be characterized by PG.

In certain diseases, the PG may be restricted to one class [24,36,67] (Table III). For instance, IgG is selectively increased in chronic active (lupoid) hepatitis and lymphogranuloma venereum with IgA and IgM being relatively normal [8,24]. IgA is selectively increased in a polyclonal fashion in certain patients with gluten-sensitive enteropathy, Aldrich syndrome, ataxia telangiectasia, familial thrombocytopenia or neutropenia, hereditary sensory neuropathy, and alcoholism. Furthermore, selective increases of polyclonal serum dimeric IgG_2-subclass, as well as glomerular deposits of IgA_2 immune complexes, have been demonstrated in Berger's disease (primary IgA nephropathy), alcoholic cirrhosis, and Henoch-Schoenlein purpura [26]. Selective polyclonal hyper-IgM is associated with early infectious hepatitis, recent viral infections, African trypanosomiasis, and neonatal or intrauterine infections.

Selective polyclonal increases of IgD may be encountered with staphylococcal skin infections, while selective polyclonal IgE increases occur with parasitic infections and the hyperimmunoglobulinemia E syndrome with undue susceptibility to infections (Buckley Syndrome) [37].

Polyclonal gammopathies are encountered much less frequently in children than in adult patients with comparable underlying diseases. For instance, during late stages of thermal burn injuries, the degree of secondary PG eventually evolving after the initial hypo-γ-globulinemia due to Ig loss (Table I) is less pronounced than in adult patients [8,24,42]. Likewise, PG developing in response to certain infections is usually less marked in children than in adults. Notable exceptions, however, do occur. For instance, toxocariasis (visceral larva migrans syndrome) may cause marked PG with increases of IgG, IgM, and IgE [24,25].

Elevated polyclonal IgM levels in cord serum may reflect nonspecifically the presence of overt or lanthanic intrauterine infections [14,15]. The fetus and the newborn can elaborate IgM earlier and at higher rates than IgG and IgA. Consequently, cord IgM concentrations are increased in almost all symptomatic neonates with congenital infections. The "TORCH" diseases—*T*oxoplasmosis, *R*ubella, *C*ytomegalovirus disease, *H*erpes simplex, and *O*thers (syphilis, listeriosis, aseptic meningitis, enteroviral infections, etc.)—are frequently accompanied by increased cord IgM. The finding of increased cord IgM in such a wide range of diseases necessitates the use of more specific diagnostic measures for these TORCH agents, including appropriate serologic tests, immunofluorescence with IgM specific antibodies, and other assays.

TABLE III. Partial List of Diseases Associated With Selective Polyclonal Increases of Serum IgG, A, M, D, or E

IgG
Chronic active (lupoid) hepatitis
IgA
Aldrich syndrome
Ataxia-telangiectasia
Gluten-sensitive enteropathy
Early hepatic cirrhosis
Alcoholic cirrhosis
Familial thrombocytopenia
Hereditary sensory neuropathy
Carcinoma of nasopharynx
Lactating women (11S-IgA)
IgM
Early hepatitis
Primary biliary cirrhosis
Recent viral infection
Neonatal or intrauterine infection (cord serum)
African trypanosomiasis
Immunodeficiency with hyper-IgM
Leprosy
Lupus erythematosus
Rheumatoid arthritis
IgD
Staphylococcal dermatitis
IgE
Aldrich syndrome
Parasitic infestation
Asthma
Idiopathic hyper-IgE (Buckley Syndrome)