50 years of Pediatric Immunology: Progress and Future - A Clinical Perspective

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Rapidly evolving advances in the field of immunology over the last few decades have impacted the practice of clinical medicine in many ways. In fact, understanding the immunological basis of disease has been pivotal in deciphering the pathogenesis of several disease processes, infective or otherwise. As of today, there is hardly any specialty of medicine which is not influenced by immunology. Pediatric rheumatological disorders, vasculitides, Human Immunodeficiency Virus (HIV) infection, Primary Immunodeficiency Diseases (PIDs) and autoimmune disorders fall under the domain of clinical immunology. This specialty is poised to emerge as a major clinical specialty in our country. The gulf between bench and bedside is narrowing down as our understanding of the complex immunological mechanisms gets better. However, a lot still needs to be done in this field as the morbidity and mortality of some of these conditions is unacceptably high in the Indian setup. A number of medical schools and institutes in the country now have the resources and the wherewithal to develop into specialized centres of clinical immunology. We need to concentrate on training more physicians and pediatricians in this field. The future is bright and the prospects exciting!

Clinical Immunology has been defined as "a clinical and laboratory discipline dealing with the study, diagnosis and management of patients with diseases or disease processes resulting from disordered immunological mechanisms, and conditions in which immunological manipulations form an important part of therapy and/or prevention" [1-3]. It is unfortunate but true, that the recognition of clinical immunology as a subspecialty in its own right has lagged far behind that of conventional 'organ-based' subspecialties as for instance cardiology, neurology, gastroenterology and the like.

Rapidly evolving advances in the field of immunology over the last few decades have impacted the practice of clinical medicine in ways which were hitherto unimaginable. In fact, understanding the immunological basis of disease has been pivotal in deciphering the pathogenesis of several disease processes, infective or otherwise [1,2]. As a result, there is hardly any specialty of medicine which can steer clear of immunology. However, for the laity, it is sometimes difficult to comprehend what exactly clinical immunology is. This is because unlike other specialties of medicine which are by definition organ driven, clinical immunology does not have a specific organ it can claim as its own!

OVERLAP WITH OTHER DISCIPLINES

Clinical immunology has an overlap with several medical disciplines and this is an important concept to understand. While specialties like cardiology, neurology and gastroenterology have a well-defined and 'loyal' clientele amongst the patients, the situation is somewhat different for clinical immunology because diseases related to the field of immunology cut across specialties as these may affect several body systems [2,3]. Accordingly, clinical immunologists are in a unique position to assess diseases in a manner no other specialty possibly can. This is one of the unique strengths of the specialty [2]. The conundrum of clinical immunology is best exemplified by systemic lupus erythematosus – the prototype collagen vascular disease [4]. While lupus can affect any system in the body and management may ordinarily and logically be considered to be system driven, it is the clinical immunologist who is in the best position to comprehend and coordinate the care of this complex multisystem disorder.

CLINICAL IMMUNOLOGY IN THE MEDICAL CURRICULUM IN INDIA

At present the undergraduate and postgraduate medical curricula in India, unfortunately, do little justice to the specialty of clinical immunology. As a result, students do not get an adequate exposure to the 'breadth and the depth' of the specialty. Their knowledge skills, therefore, leave a lot to be desired. This needs urgent remedial action because unlike what is commonly believed, disorders affecting the immune system are by no means rare conditions.

COMPONENTS OF PEDIATRIC CLINICAL IMMUNOLOGY

The following five major sets of medical conditions need the care and expertise of a pediatric clinical immunologist:

1. Pediatric rheumatological disorders

Rheumatological disorders affect nearly 2-5% of the population depending upon the criteria used to define a rheumatological disorder [4]. These figures may not look very impressive in isolation, but when extrapolated on to the country's population the numbers are indeed staggering. Rheumatology is, in many ways, the backbone of clinical immunology and an essential component of any training program in the subject. It should be noted that approximately 10-20% of patients with rheumatological disorders have onset of disease in the pediatric age group [4]. There is a crying need, therefore, to have dedicated centres of pediatric rheumatology in India. Because of the dearth of specialists in the field, it is not uncommon to see children with arthritides in our country being looked after by orthopedic surgeons even when the child with arthritis rarely needs an orthopedic intervention. This is a pity considering that the prevalence of juvenile idiopathic arthritis may be as high as 2-4 per 1000 children below 15 years of age [4].

2. Pediatric vasculitides

Amongst the vasculitides, Kawasaki disease (KD) and Henoch Schonlein Purpura (HSP) are common pediatric conditions [5-11]. We have recently shown that in the hospital setting at Chandigarh, KD has now emerged as the commonest vasculitic disorder in children [6].

Studies from Japan suggest that the incidence of KD can be as high as 239.6/100,000 children below 5 years of age [12]. KD is now the commonest cause of acquired heart disease amongst children in Japan and several Western countries [4]. A recent study from Chandigarh has projected a much lower figure than what has been computed from the Japanese data, but it is possible that majority of children with KD in India are perhaps not even being diagnosed at present [5,8,9]. This is a pity because the complications associated with KD are eminently preventable. Though the awareness of KD amongst pediatricians and physicians in India has greatly increased over the last decade, much still needs to be done in this regard [7]. It is distinctly possible that in the years to come, KD would supplant rheumatic fever as the commonest cause of acquired heart disease in India, just as it has in the West. This has serious implications for health planners in the country.

It is not often realized that HSP can have significant long-term morbidity and may not always a benign disorder of childhood. When HSP occurs in school-age children, the risk of developing serious nephritis is real and such children need close follow-up even when they do not have overt features of nephritis at onset of disease. Early recognition and prompt treatment of HSP nephritis can result in favorable outcomes [10].

3. Infection with the Human Immunodeficiency Virus

Projections from the National AIDS Control Organization (NACO) suggest that the prevalence of Human immunodeficiency virus (HIV) infection in India is showing a downward trend and is currently in the range of only 0.31% according to the Annual Report of NACO for the year 2010-11 [13]. Clearly, India has done remarkably well in the control of this epidemic. However, it is still a sobering thought that even at this low prevalence the number totals up to a staggering 2.39 million individuals. Approximately, 3.5% of these are likely to be children. Whilst patients with HIV infection can also be undoubtedly looked after by infectious disease specialists, the clinical immunologist, with his knowledge and expertise in the intricacies of the immune system, is perhaps better equipped to do so [14,15]. There are several medical schools in the country which are running clinics dedicated to the care of children with HIV infection. However, we need more pediatric clinical immunologists to deal with the complex medical problems of affected children.

4. Primary immunodeficiency diseases (PIDs)

PIDs are often perceived to be rare disorders by both physicians and the laity – this is by no means true [16-22]. Recent community based data from the Jeffrey Modell Foundation (JMF) and the Immune Deficiency Foundation (IDF), in fact, suggest that 1:1000 to 1:2000 of the population have an underlying PID. Extrapolating these data on to India's population suggest that close to a million individuals in our country may be having an underlying PID [17]. The vast majority of patients with PID in India, however, remain undiagnosed and consequently untreated [17]. There is, therefore, a crying need to create more awareness about PIDs amongst pediatricians and physicians in our country. Several of the PIDs are now eminently treatable [16].

5. Autoimmune disorders

Another aspect of clinical immunology is the study of autoimmune disorders, which encompass several major specialties like neurology, gastroenterology, hepatology, dermatology and ophthalmology. Clearly, many of these

disorders need to be managed jointly by experts in clinical immunology as well as the conventional organ based specialists [23-25]. Modern management protocols are increasingly incorporating immunomodulatory agents and biologicals for many of these conditions. The expertise and skills of the clinical immunologist are, therefore, invaluable in designing and fine-tuning of treatment strategies for a given patient, especially in children [4].

PEDIATRIC CLINICAL IMMUNOLOGY AS A SPECIALTY

Clinical immunology is different from other conventional medical specialties in many ways. For one, it has its basis in standardized laboratory tests and reproducible laboratory techniques [4,23-25]. Any fellowship program in clinical immunology, therefore, has a strong component of laboratory training. Secondly, training programs in clinical immunology can vary greatly amongst different countries [1-3]. For instance, while fellowships in clinical immunology in the United States of America often have allergy as an integral and a major component of the training, those in Europe may not give that much importance to the allergic diathesis. Similarly, some of the pediatric immunology units in the United Kingdom deal almost exclusively with PIDs. The component of rheumatology in training programs varies from center to center and depends understandably upon the profile of referred patients.

Emergence of Pediatric Clinical Immunology in India

It is heartening to note that, in India, clinical immunology is rapidly emerging as a specialty in its own right. Several medical schools/institutes have now started dedicated immunology units and outpatient clinics. However, a lot still needs to be done in this field especially as far as pediatric clinical immunology is concerned. Specialized training facilities for pediatric immunology are, at present, virtually nonexistent. As a result, there is a dearth of trained medical professionals. We still do not have a formal post-doctoral (*i.e.* DM) course in pediatric immunology anywhere in the country. This is a major lacuna which needs to be filled.

The Indian Academy of Pediatrics has a dedicated Rheumatology Chapter which has been instrumental in increasing awareness about these conditions amongst pediatricians in the country. The chapter recently held its 10th National Conference. The Indian Society for Primary Immune Deficiency (ISPID) was founded in 2010-2011 with the aim of demystifying the conundrum of PIDs amongst clinicians and laboratory scientists [17]. NACO has done yeoman service in not only halting the dreaded HIV epidemic and in facilitating the training of skilled manpower, but in also increasing the awareness about this condition amongst the medical professionals as well as in the laity [13].

Advances in Clinical Immunology

Recent advances in clinical immunology have been path breaking, especially in the field of PIDs [26-30]. The diagnosis of PIDs, in many situations, is now based on a genetic and molecular basis rather than on flow cytometry based tests, as was the case in the 1990s. The list of disorders classified under PIDs has expanded exponentially and underlying gene defects in many of these disorders have been unraveled [16]. The International Union of Immunological Societies Expert Committee on Primary Immunodeficiency Diseases recently reported on the biennial update of the classification of PIDs in 2011 [16].

The feasibility of a newborn screening program for severe combined immunodeficiency (SCID) has recently been demonstrated by the development and implementation of a mass screening programme in the state of Wisconsin, USA [26]. This is based on assay of T-cell receptor excision circles (TRECs) using real time quantitative polymerase chain reaction (PCR). Absent or low levels of TRECs strongly correlated with a diagnosis of SCID. Several other states in the USA have now similar program in place. An effort to develop a similar screening method for B cell immunodeficiencies using κ recombination excision circles (KRECs) using a similar methodology to TRECs has also been recently reported [27].

While significant advances have been made in understanding the pathogenesis of several rheumatological disorders, we are still a long way off from unraveling the etiological basis of these conditions. We are beginning to realize that the subgroups of juvenile rheumatoid arthritis may, in fact, be completely different diseases in themselves. Consequently, the therapeutic strategies for each of these conditions may need to be worked out separately. Systemic onset juvenile idiopathic arthritis may be more of an autoinflammatory condition (involving innate immunity) rather than an autoimmune condition (involving acquired immunity).

Substantial achievements have also been made in the treatment of PIDs as well as rheumatological disorders [16, 17]. Hematopoietic stem cell therapy (allogeneic, haploidentical, matched unrelated) is now well established as a treatment option for many of the cell mediated immune deficiencies like SCID and the Wiskott Aldrich syndrome (WAS). Intravenous immunoglobulin therapy has virtually revolutionized the management of

humoral immunodeficiencies like X-linked agammaglobulinemia, common variable immunodeficiency and some of the IgG subclass deficiencies [16,17]. Gene therapy trials for the treatment of PIDs have been successfully conducted in the past 2 decades particularly in Adenosine Deaminase Deficiency (ADA), X-linked SCID and WAS [28,29]. Novel approaches to gene correction with locus specific targeting (as for instance with the use of endonucleases, zinc finger nucleases and transposons) are now being developed and may soon undergo clinical trials. Generation of induced pluripotent stem cells (iPSCs) from fibroblasts of patients with PIDs is another exciting field with tremendous therapeutic potential [25].

Similarly, with the advent of monoclonal antibodies and other biologicals in the day-to-day management of rheumatological disorders [30,31], especially juvenile idiopathic arthritis and systemic lupus erythematosus, the treatment options available to the physician have undergone a sea change.

The Future of Pediatric Clinical Immunology in India

Pediatric clinical immunology is poised to emerge as a major clinical specialty in our country. The gulf between the bench and the bedside is narrowing down as our understanding of the complex immunological mechanisms gets better [32-35]. However, a lot still needs to be done in this field as the morbidity and mortality of some of these conditions is unacceptably high in the Indian setup [36]. A number of medical schools and institutes in the country now have the resources and the wherewithal to develop into specialized centres of clinical immunology. We need to concentrate on training more physicians and pediatricians in this field. The future is bright and the prospects exciting!

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REFERENCES

1. Clinical Immunology: Guidelines for its Organization, Training and Certification; Relationships With Allergology and Other Medical Disciplines-A WHO/ IUIS/IAACI Report. Clin Exp Immunol. 1993;93:484-91.
2. Shearer WT. Recognition of clinical immunology as a distinct medical subspecialty. J Allergy Clin Immunol. 2002;110:567-70.
3. Thompson RA. Clinical immunology: is it clinical science or medical practice? Clin Exp Immunol. 1993; 93:299-300.
4. Petty RE, Cassidy JT. Chronic arthritis in childhood. *In*: Cassidy JT, Petty RE, Laxer RM, Lindsley C (*Eds*), Textbook of Pediatric Rheumatology, 6th edition, Philadelphia: Saunders Elseviers; 2011. p. 505-20.
5. Singh S, Aulakh R, Bhalla AK, Suri D, Manojkumar R, Narula N, *et al*. Is Kawasaki disease incidence rising in Chandigarh, North India? Arch Dis Child. 2011;96: 137-40.
6. Singh S, Aulakh R. Kawasaki disease and Henoch Schonlein purpura: changing trends at a tertiary care hospital in north India (1993-2008). Rheumatol Int. 2010;30:771-4.
7. Singh S, Kawasaki T. Kawasaki disease - an Indian perspective. Indian Pediatr. 2009;46:563-71.
8. Singh S, Bansal A, Gupta A, Manojkumar R, Mittal BR. Kawasaki Disease – a decade of experience from North India. Int Heart J. 2005;46:679-89.
9. Singh S, Gupta MK, Bansal A, Kumar RM, Mittal BR. A comparison of the clinical profile of Kawasaki disease in children from Northern India above and below 5 years of age. Clin Exp Rheumatol. 2007;25:654-7.
10. Singh S, Dayal D, Minz RW, Joshi K, Datta U, Kumar L. Severe Henoch-Schonlein nephritis: treatment with azathioprin and steroids. Rheumatol Int. 2002;22:133-7.
11. Mahajan N, Bisht D, Dhawan V, Singh S, Minz R. Transcriptional expression and gelatinolytic activity of matrix metalloproteinases in Henoch-Schonlein purpura. Acta Paediatrica. 2010;99: 1248-52.
12. Uehara R. Epidemiologic features of Kawasaki disease in Japan, 2007-10. Pediatr Int. 2012;54:38.
13. National AIDS Control Organization. Annual Report 2010-11. Ministry of Health and Family Welfare, Government of India.
14. Singh S, Jat KR, Minz RW, Arora S, Suri D, Sehgal S. Clinical profile of 516 children affected by HIV in a tertiary care centre in Northern India: 14 years of experience. Trans Royal Soc Trop Med Hyg. 2009;103:627-33.
15. Minz RW, Singh S, Varma S, Mathuria SN, Aggrawal R, Sehgal S. Relevance of opt-out screening for HIV in emergency and pre-surgery patients in a tertiary care center in Northern India: A pilot study. Indian J Pathol Microbiol. 2010;53:287-9.
16. Al-herz W, Bousfiha A, Casanova J, Chapel H, Conley M, Cunningham-Rundles C, *et al*. Primary Immunodeficiency Diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency. Frontier Immun;2:54.doi:10.3389/fimmu.2011.00054.
17. Gupta S, Madkaikar M, Singh S, Sehgal S. Primary immunodeficiencies in India: a perspective. Ann N Y Acad Sci. 2012;1250:73-9.
18. Suri D, Singh S, Rawat A, Gupta A, Kamae C, Honma K, *et al*. Clinical profile and genetic basis of Wiskott-Aldrich syndrome at Chandigarh, North India. Asian Pac J All Immunol. 2012;30:71-8.
19. Chandrakasan S, Singh S, Dogra S, Delaunay J, Proust A, Minz RW. Wiskott-Aldrich syndrome presenting with early onset recurrent acute hemorrhagic edema and hyperostosis. Pediatr Bl Cancer. 2011;56:1130-2.
20. Rawat A, Singh S, Sharma D, Suri D, Rajwanshi A, Etzioni A. Amyloidosis in a child with Leucocyte

adhesion deficiency type-1: an unusual association. Indian J Pediatr. 2011;78:1546-8.
21. Bal A, Rawat A, Nada R, Singh S. A 12-year-old boy with X-linked agammaglobulinemia who had breakthrough infection, thrombocytopenia and acute renal failure. Natl Med J India. 2009;22: 310-6.
22. Nampoothiri S, Singh S, Nampoothiri KN, Boisson-Dupuis S, Abel L, Casanova JL. Multifocal tuberculous osteomyelitis: possible inherited interferon gamma axis Defect. Indian J Pediatr. 2012 Feb 29. [Epub ahead of print].
23. Minz RW, Kumar Y, Anand S, Singh S, Bamberi P, Verma S, Sehgal S. Antinuclear antibody positive autoimmune disorders in North India: an appraisal. Rheumatol Int. 2012;32:2883-8.
24. Minz RW, Chhabra S, Rani L, Singh S, Jindal SK, Sakhuja V. A decade long experience of anti-neutrophil cytoplasmic antibody testing in a tertiary care referral center in North India: Perspective from a developing country. Indian J Path Microbiol. 2011;54:258-63.
25. Minz RW, Chhabra S, Singh S, Radotra BD, Kumar B. Direct immunofluorescence of skin biopsy: perspective of an immunopathologist. Indian J Dermatol Venereol Leprol. 2010;76:150-7.
26. Baker MW, Grossman WJ, Laessig RH, Hoffman GL, Brokopp CD, Kurtycz DF, *et al*. Development of a routine newborn screening protocol for severe combined immunodeficiency. J Allergy Clin Immunol. 2009; 124:522-7.
27. Nakagawa N, Imai K, Kanegane H, Sato H, Yamada M, Kondoh K. *et al*. Quantification of κ-deleting recombination excision circles in Guthrie cards for the identification of early B-cell maturation defects. J Allergy Clin Immunol. 2011;128:223-25.
28. Pessach IM, Notarangelo LD. Gene therapy for primary immunodeficiencies: looking ahead, toward gene correction. J Allergy Clin Immunol. 2011;127:1344-50.
29. Fischer A, Hacein-Bey-Albina S, Cavazzana-Calvo M. Gene therapy for primary adaptive immune deficiencies. J Allergy Clin Immunol. 2011;127:1356-9.
30. Wallace CA, Giannini EH, Spalding SJ, Hashkes PJ, O'Neil KM, Zeft AS, *et al*. Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. Arthritis Rheum. 2012;64:2012-21.
31. Aggarwal P, Singh S, Suri D, Rawat A, Narula N, Manojkumar R. Rituximab in childhood lupus myocarditis. Rheumatol Int. 2012;32:1843-4.
32. Rana A, Minz R, Aggarwal R, Anand S, Pasricha N, Singh S. Gene expression of cytokines (TNF-α, IFN-γ), serum profiles of IL-17 and IL-23 in paediatric systemic lupus erythematosus. Lupus. 2012;10:1105-12.
33. Singh S, Chandrakasan S, Ahluwalia J, Suri D, Rawat A, Ahmed N, *et al*. Macrophage activation syndrome in children with systemic onset juvenile idiopathic arthritis: clinical experience from northwest India. Rheumatol Int. 2012;32:881-6.
34. Singh S, Gupta MK, Ahluwalia J, Singh P, Malhi P. Neuropsychiatric manifestations and antiphospholipid antibodies in pediatric onset lupus: 14 years of experience from a tertiary care centre of North India. Rheumatol Int. 2009;29:1455-61.
35. Salhan M, Ahluwalia J, Singh S, Minz R. Antiphospholipid antibodies in children with Henoch Schonlein Purpura – a prospective study from North India. Scand J Rheumatol. 2007;36:482-4.
36. Singh S, Dayal D, Kumar L, Joshi K. Mortality patterns in childhood lupus – 10 years experience in a developing country. Clin Rheumatol. 2002;21:462-5.