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Clinical profile of a multicenter cohort of patients with common variable immunodeficiency (CVID) from India

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Background

- Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency (PID) [1 in 10,000 to 1 in 50,000 (amongst Caucasians)]

- There is paucity of literature on CVID from developing countries including India and is limited to few case reports only
- No prevalence data on CVID from India

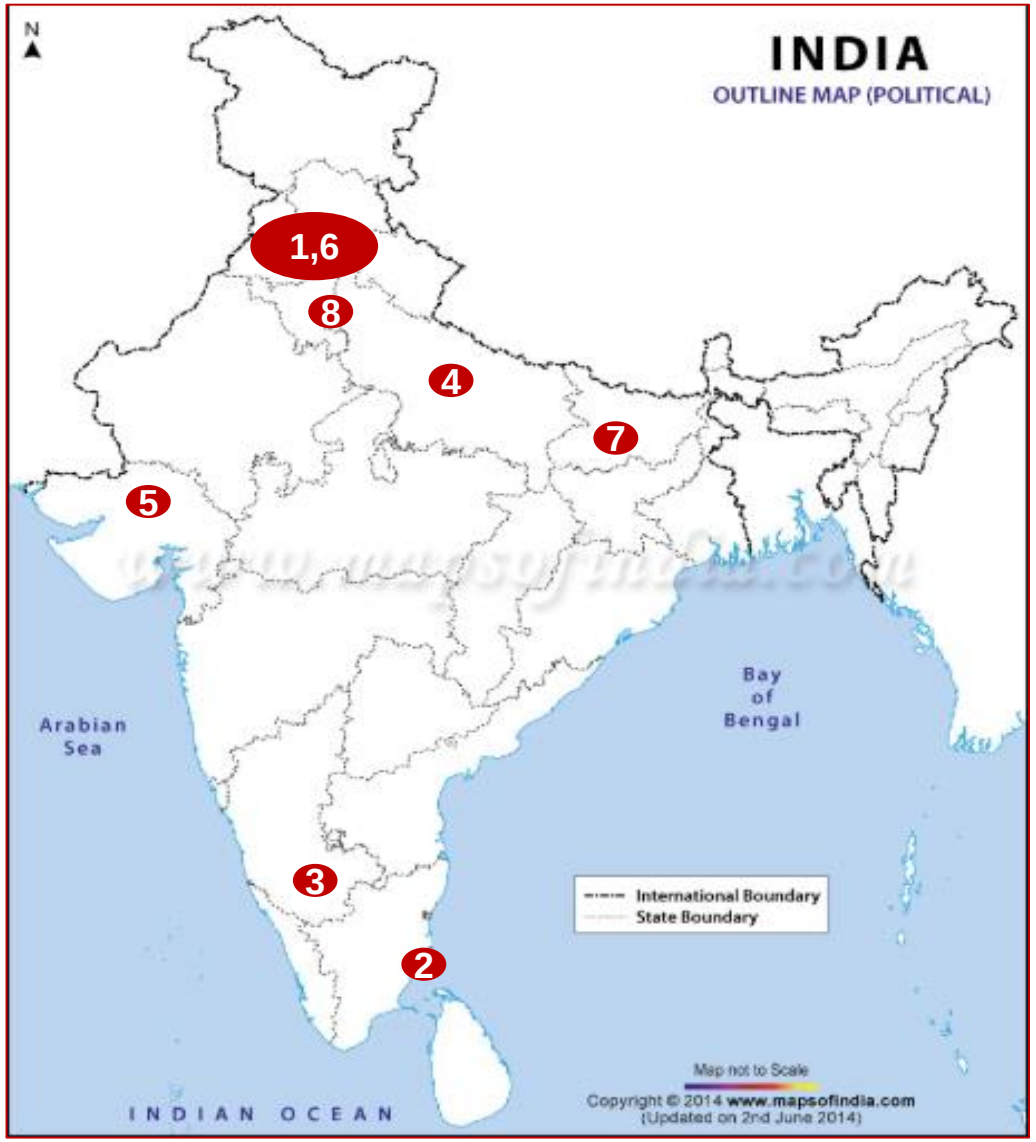
- This is the first multicenter cohort of patients with CVID from India from centers who are involved in the care of patients with immunodeficiency diseases

Patient and methods

- **An email was circulated to all centres across the country who are involved in the care of patients with PIDs**

- **Data were collected from centres who agreed to take part in this multicentre study on a predesigned data collection sheet**

Patient and methods



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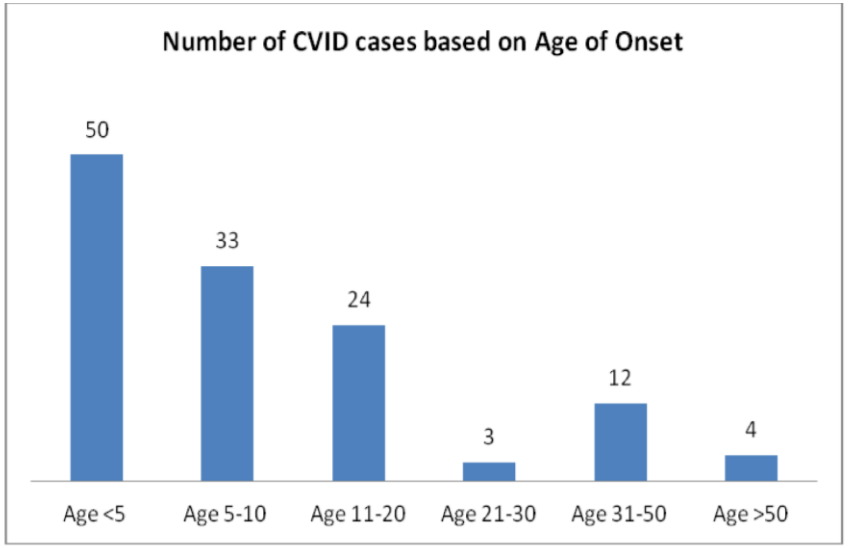
Patient and methods

- **Diagnosis of CVID was based on the European Society for Immunodeficiency (ESID) 2014 classification criteria**
- **For the purpose of this study, few patients with clinical manifestations consistent with a diagnosis of CVID with low IgA and/or low IgM with normal IgG but a low IgG2 subclass were included as probable CVID**
- **Whole exome sequencing or targeted next generation sequencing was carried out whenever possible**

Results



- In this multicentre cohort, we included **126 patients** who were diagnosed to have CVID based on the inclusion criteria
- **91 (72.22%) were males and 35 (27.77%) were females**
- History of **consanguinity in 10 patients**
- **Sibling death** in early childhood **in 5**
- **Family history of recurrent infections in 10; autoimmunity in 3 and malignancy in 3 patients**

- **91/126 (77.77%) patients had history of infections at the time of initial diagnosis**
- **A causative micro-organism could be isolated in 39/126 (31%) patients**

Results

Type of infection	No. of patients n (%)
Pneumonia	67 (53.17 %)
Diarrhoea	50 (39.68 %)
Otitis media	34 (26.98%)
Viral infections	25 (19.8%)
Varicella Zoster	9
Herpes Zoster	5
Cytomegalovirus colitis	3
Molluscum contagiosum	2
Epstein Barr Virus	2
Measles	1
Warts	1
Parvovirus	1
Hepatitis B virus	1
Herpes Simplex virus	1
Skin infections (pyoderma, skin abscess, furuncles)	19 (15.07%)

Type of infection	No. of patients n (%)
Fungal infections	13 (10.31%)
Oral Candidiasis	2
Fungal Sinusitis	2
Oral Thrush	1
Tinea Corporis	1
Esophageal candida	1
Fungal keratitis	1
Aspergilloma	1
Others	4
Meningitis	4 (3.17%)
Encephalitis	5 (3.96 %)
Septic arthritis	1 (0.8%)
Empyema	1 (0.8%)

Results

Causative microorganism	No. of patients (n=126)
Giardia lamblia	**13 (10.31%)**
Staphylococcus aureus	**6 (4.76%)**
Pseudomonas Sp.	4 (3.17%)
Mycobacterium Sp.	4 (3.17%)
Streptococcus pneumoniae	**3 (2.56%)**
Helicobacter Pylori	3 (2.38%)
Epstein Barr Virus	3 (2.38%)
SARS-CoV-2	3 (2.38%)
Enterovirus	3 (2.38%)
Cytomegalovirus	3 (2.38%)
Hemophilus influenzae	**2 (1.58%)**
Group A beta hemolytic streptococcus	2 (1.58%)
Herpes Simplex Virus	2 (1.58%)
Cryptosporidium parvum	2 (1.58%)
Candida Sp.	2 (1.58%)
Pneumocytis jiroveci	1 (0.8%)
Aspergillus sp.	1(0.8%)
Nocardia sp.	1 (0.8%)

	No bronchiectasis (n=97)	Bronchiectasis (n=29)	p value	No autoimmunity (n=83)	Autoimmunity (n=43)	p value
Mean age of onset	12.56±14.9	11.71±11.46	0.79	11.91±13.4	13.15±15.68	0.66
Mean age at diagnosis	19.3±16.4	21.1±11.96	0.61	19.1±15.1	20.8±16.17	0.57
Mean delay in diagnosis ± SD	6.75±6.54	9.07±6.27	0.094	7.05±6.61	7.88±6.46	0.511
Mean IgG (mg/dL)	166.68±157.97	357.38±310.53	**<0.001**	338.29±367.54	300.29±248.52	**0.021**
Mean IgM (mg/dL)	53.70±123.96	69.99±100.97	**0.005**	52.25±78.14	76.25±119.98	**0.010**
Mean IgA (mg/dL)	36.08±77.18	48.91±81.86	**0.030**	67.77±113.12	34.67±54.05	0.130
Recurrent infections	72/97 (74.22%)	25/29 (86.20%)	**<0.001**	58/83 (69.87%)	33/43 (76.74%)	**0.02**
Pneumonia	38/97 (39.17%)	29/29 (100%)	**<0.001**	47/83 (56.62%)	20/43 (46.51%)	0.29
Otitis Media	3/97 (3.09%)	14/29 (48.27%)	**<0.001**	22/83 (26.50%)	11/43 (25.58%)	0.912
Diarrhoea	30/97 (30.92 %)	20/29 (68.96%)	**<0.001**	32/83 (38.55%)	18/43 (41.86%)	0.37
Fungal infections	6/97 (6.18 %)	7/29 (24.13%)	**0.016**	6/83 (7.22%)	4/43 (9.30 %)	**0.02**
Viral infections	15/97 (15.46 %)	10/29 (34.48%)	0.119	11/83 (13.25%)	14/43 (32.55%)	0.06
Skin infections	11/97 (11.34%)	7/29 (24.13%)	0.176	11/83 (13.25 %)	7/43 (16.27%)	0.41
CNS manifestations	6/97 (6.18 %)	2/29 (6.89 %)	0.567	2/83 (2.40%)	6/43 (13.95%)	**0.02**
Autoimmunity	35/97 (36.08 %)	8/29 (27.58%)	0.26	-	-	-

Results

Five patients (3.2%) developed malignancy

- Hodgkin lymphoma in 1
- non-Hodgkin lymphoma in 3
- Carcinoma lung in 1

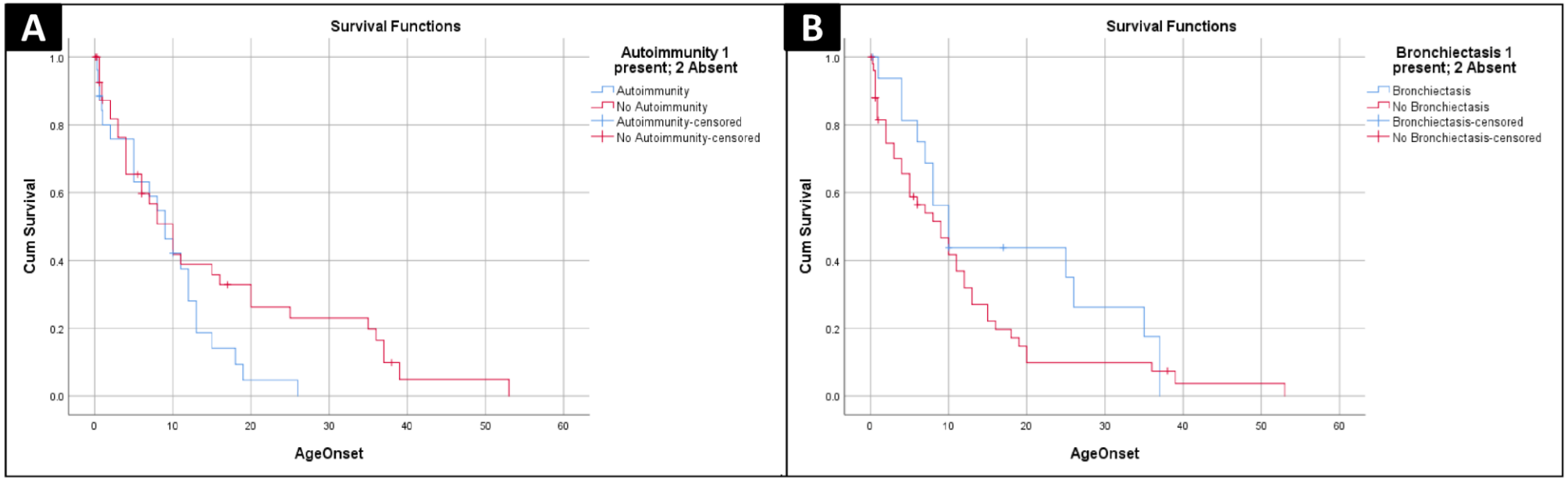
Whole exome sequencing or targeted next generation sequencing could be performed in 33 patients
Of these, **13 patients (39%) were found to have a pathogenic variant**

- **Lipopolysaccharide-responsive and beige-like anchor (LRBA) (n=2)**
- **SH2 Domain Containing 1A (SH2D1A) (n=2)**
- **Syntaxin binding protein- 2 (STXBP2) (n=2)**
- X-Linked Inhibitor Of Apoptosis (XIAP) (n=1)
- IFN regulatory factor 2 binding protein 2 (IRF2BP2) (n=1)
- Dedicator of cytokinesis 2 (DOCK2) (n=1)
- Activation Induced Cytidine Deaminase (AICDA) (n=1)
- Zinc Finger And BTB Domain Containing 24 (ZBTB24) (n=1)
- DNA cross-link repair 1C (DCLRE1C) (n=1)
- Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Delta (PIK3CD) (n=1)

One patient was suspected to have **nuclear factor-kappa B Essential Modulator (NEMO) deficiency**. However, whole exome sequencing was normal
Two siblings were clinically suspected to have **tRNA Nucleotidyl Transferase 1 (TRNT1) deficiency** (hypogammaglobulinemia and retinitis pigmentosa) However, genetic analysis could not be carried out for this family

Treatment and outcome

- Of the 126 patients, **84 (66.66%) could be initiated on replacement intravenous immunoglobulin (IVIg) therapy** (dose: 400 mg/kg every 3-4 weeks)
- There was a **mean delay of 6.82 years in initiating IVIg therapy** from the time of diagnosis
- **Co-trimoxazole prophylaxis was given to nearly all patients**
- Immunosuppressant therapy for autoimmune manifestations was given to 29/126 patients (24.78%)
- **Nine patients died** in the cohort till the time of data collection
- Cause of death was pneumonia (n=2), brain abscess (n=2), carcinoma lung (n=1) and encephalitis (n=1)
- Three patients died at home and cause could not be ascertained
- Patients were followed up over a median duration of 53 months (range: 6 months to 20 years)



Kaplan-Meir survival analysis (x axis shows follow up duration in months, y axis shows survival

A) Survival analysis for patients with **CVID with and without bronchiectasis**

B) Survival analysis for patients with **CVID with and without autoimmunity There are no significant differences in the survival in these groups**

Cox regression analysis showed that presence of fungal infections, central nervous system infections and tuberculosis significantly predicted the risk of mortality (p value 0.018, 0.023 and 0.021 respectively)

Strengths and limitations

- **Strengths:**
  - **This is the largest cohort of patients with CVID from India and data were collected from several centers**
  - However, **this is a gross underestimate of the actual number of patients with CVID in India** as several centers could not share their data and large majority of patients still remain undiagnosed

- **Limitations:**
  - Some of the patients were lost to follow-up
  - We did not have complete information on trough IgG levels for several patients and therefore a correlation of trough IgG levels with clinical profile could not be carried out
  - Genetic etiology could not be evaluated in most patients and a detailed flow cytometry for B cell immunophenotyping was not available

How do we overcome the limitations?

- We have now prepared a comprehensive panel for carrying out detailed flow cytometry for patients with CVID

- The genetic and epigenetic studies for most patients with CVID are underway

Ms. Sanchi
PhD Student, Allergy Immunology Laboratory

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Collaborating institutes in India who shared their data