News and Views

Presentation on Molecular Genetic Approach in Diagnosing Childhood Primary Immunodeficiency Disease (PID) Attending Six Major Hospitals in Bangladesh

Dr. Sudipta Roy, ARM L Kabir and Dr. Kazi Selim Anwar

Background

PIDs are a heterogeneous group of adaptive and innate immune system inherited disorders. However, these disorders remain under-recognized and under-reported in several developing countries due to a lack of awareness among physicians and the non-availability of diagnostic facilities.

Abstract

On this ongoing study 42 cases were enrolled, PID screening positive-31, clinical exome sequencing was done in 13 cases yielded pathogenic mutations were found in 3 cases, likely pathogenic in 2 cases and significance in 7 cases. Genetically of three pathogenic genes one each of SCID Gene- IL2RG (-), X-Linked agammaglobulinemia GeneBTK (-) AND immunodeficiency-8 Gene-CORO1A (+) . Two of likely pathogenic are Severe congenital neutropenia-2 Gene-GFI1 (-) and Vici syndrome, Gene-EPG5 (-).

Objective:

To confirm the diagnosis of clinically suspected screening-positive PIDs in Bangladeshi children using molecular genetics.

Methodology

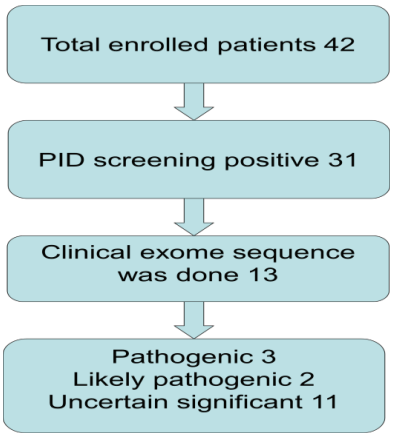
This is an ongoing longitudinal observational multicenter study in the pediatric department of 6 hospitals in Dhaka city funded by integrated health science research and development fund activity, Ministry of health and family welfare, Bangladesh over 2 years (September 2022 to August 2023). Study population -50. Children under 18 years with recurrent or persistent infections (3 or more) were enrolled. Exclusion criteria: chronic steroid ingestion, AIDS, PEM, NS, Leukemia etc.). PID screening tests (CBC, Serum antibody IgA, IgG, IgM, IgE and Lymphocyte Subset analysis), infection screening (CXR, MT, Gastric lavage etc.) were done. Clinical exome sequencing was performed in selected screening positive PID cases in Med Genome Labs Ltd., Bangalore, India for genetic analysis. Interim analysis was done after six months of study.

Result

Distribution of preliminary selected patients (42) fulfilling the inclusion criteria:

Conclusions

In the literature review, very few studies on PIDs have been published from Bangladesh and no molecular genetic analysis has been conducted yet. Our study shows 38% of clinically suspected patients have genetically confirmed PID. Large scale study is required to understand the molecular basis of PIDs in Bangladeshi children.



Variable	Frequency
Age (Months)	31.29 ± 39.35
Sex	
Male	20 (71%)
Female	9 (29%)
M: F	2.2:1
Consanguinity	16 (51.6%)
H/O Sib death	5 (16.1%)
Affected Sib	4 (12.9%)
Mean age of onset (Months)	7.41 ± 9.25
Mean age of Diagnosis (Months)	30.56 ± 39.69

Table 1. Demographic profile of the study cases.

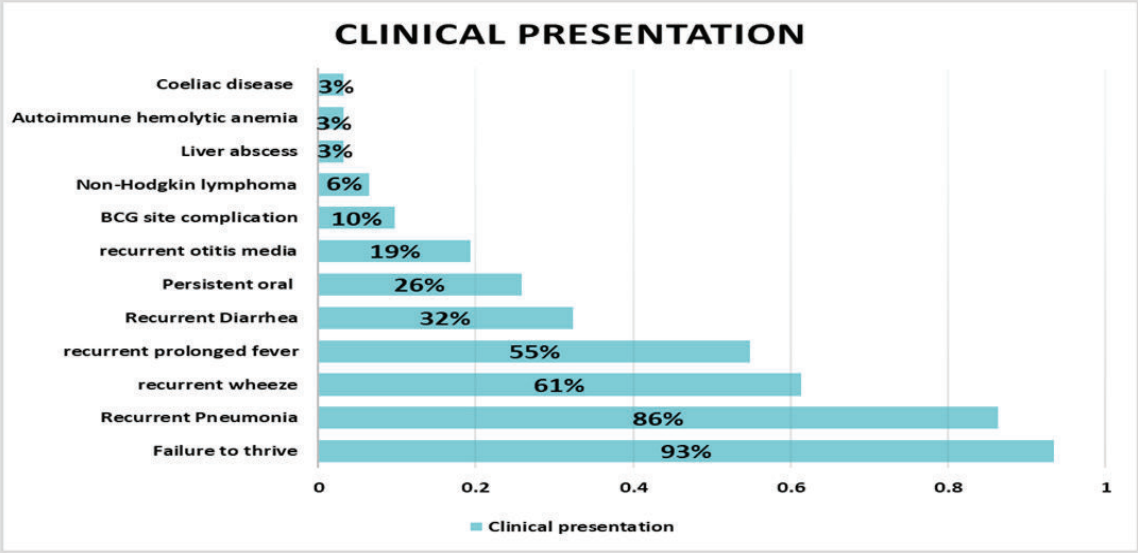


Chart 1 : The clinical presentation of PID patients

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ABSTRACT

On this ongoing study 42 cases were enrolled, PID screening positive -31, clinical exome sequencing was done in 13 cases yielded pathogenic mutations were found in 3 cases, likely pathogenic in 2 cases and uncertain significance in 7 cases. Genetically of three pathogenic genes one each of SCID Gene-IL2RG(-), X-linked agammaglobulinemia GeneBTK(-) and Immunodeficiency-8 Gene-CORO1A(+). Two of Likely- pathogenic are Severe congenital neutropenia-2 Gene-GFI1(-) and Vici syndrome, Gene-EPG5 (-)

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RESULTS

Distribution of preliminary selected patients (42) fulfilling the inclusion criteria:

Total enrolled patients 42

↓

PID screening positive 31

↓

Clinical exome sequence was done 13

↓

Pathogenic 3
Likely pathogenic 2
Uncertain significant 11

RESULTS

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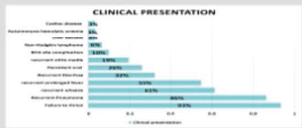

Chart 1. Bar Chart showing the clinical presentation of PID patients.

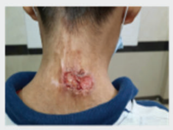

Figure 1. Chronic Nocardia infection in Hyper IgE syndrome.

Figure 2. BCG site abscess in SCID.

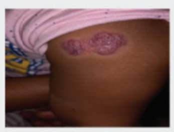

Figure 3. Exaggerated BCG response in NK cell deficiency.

Figure 4. Subcutaneous emphysema.

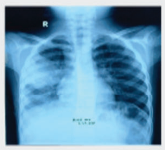

Figure 4. CXR showing consolidation (rt. Lung) in Hyper IgE syndrome.

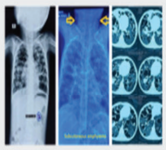

Figure 5. Bilateral cystic lesions & subcutaneous emphysema & Multiple cystic lesions in severe congenital neutropenia.

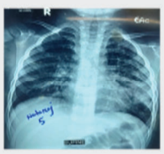

Figure 6. CXR showing bilateral consolidation in Bruton's agammaglobulinemia(X-linked).

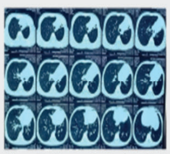

Figure 7. CT scan showing left-sided extensive bronchiectasis in Bruton's agammaglobulinemia (X- linked).

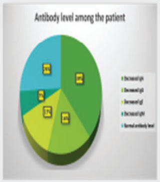

Chart 2. Pie chart showing antibody levels among the patient.

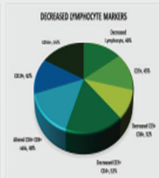

Chart 3. Pie chart showing the status of T cell, B cell, NK cell.

Findings of Clinical Exome Sequencing

SN	Gene(Transcript) & Location	Variant	Zygosity	Disease(OMIM)	Inheritance	Classification
01	IL2RG (-)(ENST00000374202.7) Exon 8	c.[illegible]del (p.[illegible])	Hemizygous	Severe combined immunodeficiency (OMIM#300400); Combined immunodeficiency (OMIM#312863)	X-linked recessive	Pathogenic
02	BTK (-)(ENST00000308731.8) Exon 9	c.[illegible] (p.[illegible])	Hemizygous	X-linked agammaglobulinemia/hypogammaglobulinemia ([illegible])	X-linked recessive	Pathogenic
03	CORO1A(+) (ENST00000219150.1) Intron 7	c.[illegible] (?splice site)	Homozygous	Immunodeficiency-8	Autosomal recessive	Pathogenic
04	EPG5 (-) (ENST00000282041.11) Exon 37	c.[illegible] (p.[illegible])	Homozygous	Vici syndrome (OMIM#242840)	Autosomal recessive	Likely Pathogenic
05	GFI1 (-) (ENST00000294702.6) Exon 4	c.[illegible]delinsCTACAAG (p.[illegible])	Heterozygous	Severe congenital neutropenia 2 (OMIM#613107)	Autosomal dominant	Likely pathogenic

Table 2. Table showing Pathogenic or likely pathogenic mutation in 5 patients.

SN no	Name of gene & location	Variant	Zygosity	Disease	Inheritance	Classification
01	TCF3(-) ([illegible]) Exon 7	c.[illegible] (p.[illegible])	Heterozygous	Agammaglobulinemia-8A; Agammaglobulinemia -8B	Autosomal recessive	Uncertain Significance
02	LIG1(-) ([illegible]) Exon 11	c.[illegible] (p.[illegible])	Heterozygous	Immunodeficiency -96	Autosomal recessive	Uncertain Significance
03	DNAH11 (+) ([illegible]) Exon 40	c.[illegible] (p.[illegible])	Heterozygous	Primary ciliary dyskinesia-7	Autosomal recessive	Uncertain Significance
04	JAK3 (-) ([illegible]) Exon 19	c.[illegible] (p.[illegible])	Heterozygous	T cell-negative (T-), B cell-positive (B+), natural killer cell-negative (NK-) severe combined immunodeficiency	Autosomal recessive	Uncertain Significance
05	MCM4 (+) ([illegible]) Exon 14	c.[illegible] (p.[illegible])	Heterozygous	Immunodeficiency 54	Autosomal recessive	Uncertain Significance
06	ZAP70 (+) ([illegible]) Exon 9	c.[illegible] (p.[illegible])	Heterozygous	Infantile-onset multisystem autoimmune disease-2	Autosomal recessive	Uncertain Significance
07	IL12RB1 (-) ([illegible]) Exon 5	c.[illegible] (p.[illegible])	Heterozygous	Immunodeficiency 30	Autosomal recessive	Uncertain Significance
08	CD40LG (+)([illegible]) Exon 5	c.[illegible] (p.[illegible])	Heterozygous	X-linked immunodeficiency with hyper IgM type1	X-linked recessive	Uncertain Significance
09	C7 (+) ([illegible]) Intron 15	c.[illegible] (5' splice site)	Heterozygous	C7 deficiency	Autosomal recessive	Uncertain Significance
10	LRBA (-) ([illegible]) Exon 22	c.[illegible] (p.[illegible])	Heterozygous	Common variable immunodeficiency 8 with autoimmunity	Autosomal recessive	Uncertain Significance
11	TAP1(-) ([illegible]) Exon 9	c.[illegible] (p.[illegible])	Homozygous	Bare lymphocyte syndrome type I	Autosomal recessive	Uncertain Significance

Table 3. Table showing mutation of uncertain significance in 11 patients.

CONCLUSIONS

In the literature review, very few studies on PIDs have been published from Bangladesh and no molecular genetic analysis has been conducted yet. Our study shows 38% of clinically suspected patients have genetically confirmed PID. Large scale study is required to understand the molecular basis of PIDs in Bangladeshi children.