ORIGINAL ARTICLE

TO DETERMINE THE FREQUENCY OF ALDEHYDE DEHYDROGENASE TYPE 2 (ALDH2) DEFICIENCY IN APLASTIC ANAEMIA: A SINGLE CENTER EXPERIENCE FROM PAKISTAN

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Background: Aplastic anaemia is a rare bone marrow failure syndrome and is defined by pancytopenia associated with a hypo-cellular bone marrow with no increase in reticulin and the absence of any abnormal infiltrate. The objective of the study was to determine the frequency of Aldehyde Dehydrogenase type 2 (ALDH2) deficiency in patients with Aplastic Anaemia and investigate its correlation with patient and disease characteristics. It was a descriptive cross-sectional study conducted at Armed Forces Bone Marrow Transplant Centre Rawalpindi from 01-08-2022–01-02-2023, over 6 months. **Methods:** A total of 56 patients who were diagnosed with aplastic anaemia during this period, fulfilling inclusion criteria were enrolled. Patients were genotyped as GG (homozygous) and GA (heterozygous). GG had normal ALDH2, while GA were patients with ALDH2 deficiency. Data was collected on the patient's demographics, type and severity of anaemia, type of hematopoietic stem cell transplant (HSCT) and frequency of ALDH2 deficiency. Results were analyzed for ALDH2 deficiency and its correlation with patient and disease characteristics was investigated. **Results:** A total of 56 patients were included in the study. The median age of the patients was 28 years (20–39). According to the type of aplastic anaemia, 2 (3.6%) had Fanconi anaemia and 54 (96.4%) had acquired aplastic anaemia. In our study, 18 (32.1%) patients had undergone HSCT while the remaining 38 (67.9%) could not undergo HSCT. The frequency of the presence of ALDH2 deficiency was 2 (3.6%). There was no statistically significant correlation between the frequency of ALDH2 deficiency with variables like gender, age distribution, type of aplastic anaemia, the severity of aplastic anaemia and hematopoietic stem cell transplant. **Conclusion:** We concluded from our study the frequency of ALDH2 was rare in patients with aplastic anaemia. There was no statistically significant correlation between the frequency of ALDH2 deficiency with variables like gender, age distribution, type of aplastic anaemia, the severity of aplastic anaemia and hematopoietic stem cell transplant.

Keywords: Aplastic anaemia; Fanconi anaemia; Aldehyde Dehydrogenase type 2 (ALDH2); Hematopoietic stem cell transplant

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INTRODUCTION

Aplastic anaemia is a rare bone marrow failure syndrome and is defined by pancytopenia associated with a hypo-cellular bone marrow with no increase in reticulin and in the absence of any abnormal infiltrate.[1] It can be inherited or acquired. Aldehyde dehydrogenase (ALDH) enzymes belong to a 19-isoenzyme family of proteins which are required to oxidize aldehydes to their respective acidic derivatives. Intracellular aldehydes can be derived from both exogenous and endogenous sources. They can lead to DNA damage by forming inter-stand cross-links (ICL) between DNA strands and hence play an important role in the detoxification of aldehydes including acetaldehydes, that are produced during the metabolism of alcohol and other substances.[2] Aldehyde dehydrogenase type 2 (ALDH2) deficiency affects 8% of the world population, and individuals of East Asian descent have the highest prevalence (35–45%).[3] ALDH2 is one of the 19 ALDH and it plays a key role in catalyzing the oxidation of toxic cellular aldehydes. The ALDH2*2 mutant is produced when an adenine is substituted for a guanine (rs671) and a point mutation occurs at nucleotide 1459. This alters the amino acid 487 of the mature protein, with lysine substituted for glutamic acid. The structural instability of the ALDH2*2 mutant results in reduced ALDH2 activity.[4] Therefore, it is possible that ALDH2*2 and reduced ALDH2 activity increases susceptibility to bone marrow failure.

An extensive literature search showed that different studies on aplastic anaemia in Pakistan have been conducted,[5–8] however, the frequency of Aldehyde dehydrogenase type 2 (ALDH2) deficiency in Aplastic anaemia has not yet been documented in Pakistan.

Considering the significance of this association, we aim to do this study to document the frequency of aldehyde dehydrogenase type 2 (ALDH2) deficiency in patients with Aplastic anaemia in our population.

The objective was to determine the frequency of Aldehyde Dehydrogenase type 2 (ALDH2) deficiency in patients with Aplastic Anaemia and investigate its correlation with patient and disease characteristics.

MATERIAL AND METHODS

This descriptive cross-sectional study was conducted at Armed Forces Bone Marrow Transplant Centre (AFBMTC) Rawalpindi from 01-08-2022—01-02-2023, over a period of 6 months. Male and female patients of all age groups, regardless of their treatment status were included in this study. Patients who did not give consent were excluded.

Formal approval was taken from the Ethical Review Committee of the Armed Forces of Bone Marrow Transplant Center (AFBMTC). Informed written consent was taken from the patients and data was collected while respecting the anonymity of the individual participants. After taking informed consent a thorough history was taken and as much as 03ml samples of Peripheral Blood/Bone marrow were collected in EDTA tubes. DNA were extracted from the sample followed by conventional PCR amplification. Stained and purified PCR products were loaded on a genetic analyzer plate that showed the results of gene sequencing. Patients were genotyped as GG (homozygous) and GA (heterozygous). GG had normal ALDH2, while GA were patients with ALDH2 deficiency (Figure-1). Data was collected on the patient's demographics, type and severity of anaemia, type of hematopoietic stem cell transplant (HSCT) and frequency of ALDH2 deficiency.

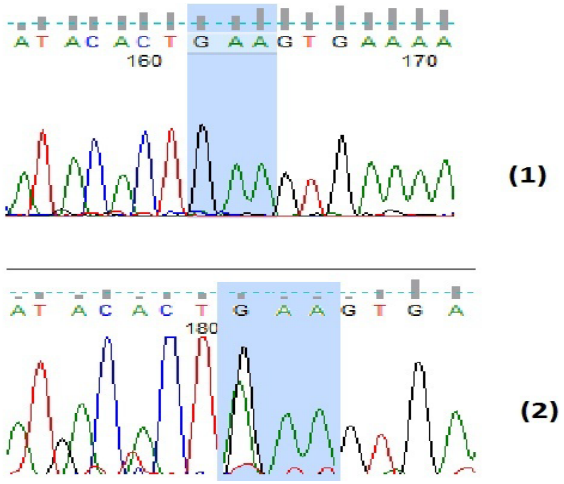

Figure-1: Showing genotype of patients (1) Genotype GG (homozygous)- single peak in G region (2) Genotype GA (heterozygous)- double peak in G region

Data was entered and analyzed using SPSS Version 25.0. Frequencies/percentage was calculated for qualitative variables like gender, type and severity of aplastic anaemia, HSCT and presence of ALDH2 deficiency. Median and SD were calculated for quantitative variables like age. The effects made from age, gender and type of aplastic anaemia, severity of aplastic anaemia and hematopoietic stem cell transplant (HSCT) were controlled by stratification. Post-stratification Pearson Chi-square was applied. A *p*-value of ≤0.05 was considered significant. Results were expressed in charts, graphs and tables.

RESULTS

A total of 56 patients were included in the study. The median age of the patients was 29 years (22–38). According to the type of aplastic anaemia, 2 (3.6%) had Fanconi anaemia (FA) and 54 (96.4%) had acquired aplastic anaemia. On the basis of severity, 32 (57.1%) were non-severe aplastic anaemia (NSAA), 19 (33.9%) were severe aplastic anaemia (SAA) and 5 (8.9%) were very severe aplastic anaemia (VSAA) (Table-1). Allogenic hematopoietic stem cell transplant (HSCT) was done in 18(32.1%) patients while the remaining 38 (67.9%) could not undergo HSCT (Figure 2). The frequency of the presence of ALDH2 deficiency was 2 (3.6%) [Figure-3]. In our study, there was no statistically significant correlation between the frequency of ALDH2 deficiency with variables like gender, age distribution, type of aplastic anaemia, the severity of aplastic anaemia and HSCT (Table-2).

Table-1: Patients Characteristics

Characteristics	n= 56		Percentage
Median age	29 years (22-38)		
Gender	Male	40	71.4
	Female	16	28.6
Age distribution (years)	0-20	11	9.8
	21-40	33	29.5
	41-60	4	3.5
	61-80	8	7.1
Type of aplastic anaemia	Fanconi anaemia	2	3.6
	Acquired aplastic anaemia	54	96.4
The severity of aplastic anaemia	NSAA	32	57.1
	SAA	19	33.9
	VSAA	5	8.9

Table-2: Association of ALDH2 deficiency with different variables

Variable	n=2		*p*-value
Severity of anaemia	NSAA	2	0.459
	SAA	0	
	VSAA	0	
Age distribution(years)	0-20	0	0.487
	21-40	1	
	41-60	0	
	61-80	1	
Gender	Male	1	0.495
	Female	1	
Type of anaemia	Fanconi anaemia	0	0.782
	Acquired aplastic anaemia	2	
HSCT	Yes	0	0.322
	No	2	

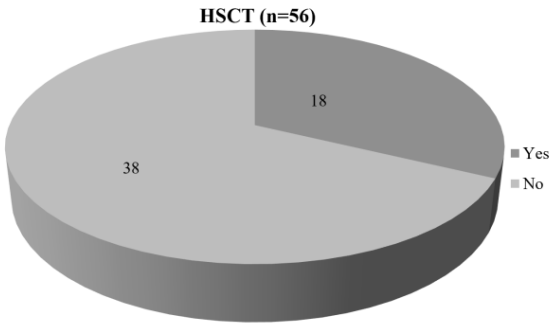

Figure-2: Number of allogenic hematopoietic stem cell transplant

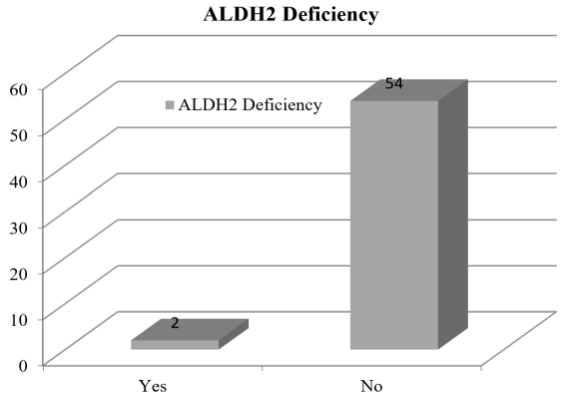

Figure-3: Presence of ALDH2 deficiency

DISCUSSION

Aldehyde dehydrogenase (ALDH) deficiency is a rare genetic disorder. It affects the body's ability to break down alcohol and other toxic substances. This condition can also cause various health complications, including liver disease, oesophageal cancer, Alzheimer's disease and aplastic anaemia. It can also contribute to aplastic anaemia by decreasing the body's ability to detoxify acetaldehyde, a consequence of alcohol metabolism. Acetaldehyde can harm bone marrow cells, resulting in a decrease in blood cell synthesis.[2]

The frequency of ALDH2 deficiency varies among different populations, but it is estimated that up to 35–40% of people of East Asian descent have a deficiency in this enzyme.[3] However, in our study the frequency of ALDH2 deficiency was 3.6%. We had an extensive literature search and could only find very few studies showing the relation between ALDH2 deficiency and aplastic anaemia.

Hira *et al* (2013) determined the ALDH2 genotype of 42 Japanese FA patients. They found that ALDH2 deficiency accelerated bone marrow failure. The patients with complete ALDH2 deficiency experienced bone marrow failure within the first 7 months of life.[9] Kawashima *et al.* (2019) conducted a study on 79 patients. The severity of the disease was categorized as very severe (n=10), severe (n=40) and non-severe (n=29). On the basis ALDH2 genotyping, 40 children were genotyped as GG, 29 as GA, and 10 as AA. They concluded that in children having AA the age of diagnosis was significantly younger (median 2 years, range 0·83–6 years) as compared with the children having GG (median 9.5 years, range 1.6–15 years) and GA (median 9 years, range 1–14 years).[10] Both these studies are in contrast to our study as we could not find any co-relation of ALDH2 deficiency with variables like the severity of anaemia, type of anaemia or age distribution of patients.

Currently, there is no published data from Pakistan related to the frequency of ALDH2 deficiency in aplastic anaemia. There is little evidence to suggest that ALDH2 deficiency may be a risk factor for the development of aplastic anaemia. Further research is therefore required to fully understand the role of ALDH2 deficiency in the development of aplastic anaemia.

CONCLUSION

We concluded from our study that the frequency of ALDH2 was rare in patients with aplastic anaemia. There was no statistically significant correlation between the frequency of ALDH2 deficiency with variables like gender, age distribution, type of aplastic anaemia, severity of aplastic anaemia and HSCT.

Further research is needed to better understand the mechanisms underlying this association and to explore potential therapeutic strategies for individuals with ALDH2 deficiency and aplastic anaemia. Future studies may shed light on the mechanisms underlying this association and may pave the way for novel therapeutic strategies for patients with ALDH2 deficiency and aplastic anaemia.

Limitation of study: Our study had many limitations. It was conducted on a small scale with a smaller number of patients. It was a single-centre study and should be recommenced at the national level with various transplant centres contributing their data under a unified registry.

Conflicts of interest: This study has no conflict of interest to be declared by any author.

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AUTHORS' CONTRIBUTION

NS: Acquisition, drafting work and agreement to be accountable for all aspects of work. MAK, RI: Conception and design of the work. ZA: Analysis and data interpretation. HJ, JR: Critically revision for important intellectual content. QC, TG: Final approval of the version to be published.

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