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Phenylketonuria in Western Libya: Demographic Patterns, Diagnostic Delays, and Neurodevelopmental Outcomes

Khadija Mohamed Alasayh[1], and AsmaAbdullwahab Khalif[2]

[1]Higher institute of science and medical technology/Abuslim, Tripoli, Libya

[2]Higher institute of science and medical technology/Abuslim, Tripoli, Libya

*Corresponding author:khadija.alasayh@gmail.com

الفينايل كيتون يوريا في غرب ليبيا: الأنماط الديموغرافية، التأخّر في التشخيص، والنتائج النمائية العصبية

خديجة محمد السايح*[1]، أسماء عبدالوهاب خليفة[2]

[1] المعهد العالي للعلوم والتقنيات الطبية/أبوسليم, طرابلس, ليبيا

[2]المعهد العالي للعلوم والتقنيات الطبية/أبوسليم, طرابلس, ليبيا

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Abstract:

Phenylketonuria (PKU) is a rare autosomal recessive metabolic disorder characterized by a deficiency in phenylalanine hydroxylase (PAH), leading to high concentrations of phenylalanine in the blood which can cause brain damage. This research focuses on evaluating the demographic patterns of PKU in the western region of Libya and assessing the effect of early intervention on neurodevelopmental outcomes. Data collection was done at El Galaa Hospital and subsequently analyzed using SPSS. Early diagnosis and dietary intervention to lower blood phenylalanine concentrations are crucial to help prevent the cognitive and behavioural complications that are associated with this disorder.

Keywords: Phenylketonuria; autosomal recessive; western region of Libya.

الملخص:

فينايل كيتون بوريا(PKU) هو اضطراب أيضي نادر يُورث بطريقة متنحية مرتبطة بالصبغيات الجسمية، ويتميّز بنقص إنزيم الهيدروكسيلاز للفينيل ألانين(PAH) ، مما يؤدي إلى تراكم كميات عالية من الفينيل ألانين في الدم، وهو ما قد يسبب تلفًا في الدماغ. تركز هذه الدراسة على تقييم الأنماط الديموغرافية لداء الفينيل كيتون في المنطقة الغربية من ليبيا، بالإضافة إلى دراسة تأثير التدخل المبكر على النتائج النمائية العصبية. تم جمع البيانات في مستشفى الجلاء، ثم تحليلها باستخدام برنامج SPSS. يُعد التشخيص المبكر والتدخل الغذائي لخفض تركيز الفينيل ألانين في الدم أمرًا بالغ الأهمية للوقاية من المضاعفات الإدراكية والسلوكية المرتبطة بهذا الاضطراب.

Introduction

Phenylketonuria (PKU) is the most common inborn error of amino acid metabolism, caused by pathogenic variants in the phenylalanine hydroxylase (PAH) gene. This genetic defect leads to a deficiency in the PAH enzyme,

which is responsible for converting the amino acid phenylalanine (Phe) into tyrosine (Hillert et al., 2020). Without a functional enzyme, Phe accumulates to toxic levels in the blood and brain, resulting in severe and irreversible intellectual disability, seizures, and other neurological problems if left untreated (Jafari et al., 2023).

Fortunately, the devastating consequences of PKU can be prevented. The introduction of routine newborn screening (NBS) programs, which began over 50 years ago, allows for the detection of PKU within the first days of life through a simple heel-prickblood test (NORD, n.d.). Early diagnosis followed by the implementation of a lifelong low-phenylalanine diet enables individuals with PKU to achieve normal growth and cognitive

The global prevalence of PKU varies significantly across different ethnic populations. While relatively low in some Asian populations, it is not ably higher in others, such as in Turkey (1 in 2,600) and Ireland (1 in 4,500). A comprehensive meta-analysis identified the Middle East/North Africa (MENA) region as having the highest regional birth prevalence of PAH deficiency in the world. The highest regional birth prevalence was observed in the Middle East/North Africa, with 1.18 (95% CI 0.64–1.87) cases per 10,000 births (Foreman et al., 2021). This is significantly higher than the estimated global average of 0.64 per 10,000 births. (vanSpronsen et al., 2021)

This elevated prevalence is strongly linked to the high rates of consanguineous marriage common in the region. Consanguinity increases the likelihood of off spring inheriting two copies of a recessive gene variant from a common ancestor (Tadmouri et al., 2009). Studies from neighbouring countries confirm this trend, with consanguinity rates among parents of PKU patients reported as 57% in Egypt, 86.6% in Iran, and 100% in one Iraqi cohort (Al-Arrayed et al., 2018). This regional backdrop sets a high-risk context for PKU in Libya.

Despite the high-risk regional context, there is a profound lack of data on PKU in Libya. Multiple sources explicitly state that no national newborn screening program for PKU has been implemented, and consequently, there are no published records of its national incidence (El-Gharbi et al., 2010).Systematic reviews on PKU prevalence in the Arab world and North Africa frequently list Libya among countries with no available data, alongside nations like Algeria, Syria, and Yemen (Al-Arrayed et al., 2018). This information vacuum makes it impossible to quantify the true burden of the disease on the Libyan population and hinders the development of targeted public health policies.

In the absence of national data, the most significant insights come from a 12-year hospital-based study conducted at the El-Khadra Teaching Hospital in Tripoli between 2001 and 2012. The study investigated 107 children with various inbornerrors of metabolism (IEM). While not focused solely on PKU, it provided critical demographic and prevalence indicators. The study found a birthp revalence for all IEMs of 1:1,458 live births at that hospital, and more specifically, a prevalence for amino acid disorders (the categoryincluding PKU) of 1:6,158 (El-Moghrabi et al., 2014).Crucially, the study reported an exceptionally high consanguinity rate of 86.9% among the parents of children withIEMs, confirming that this major risk factor is highly prevalent in the Libyan population.

Materials and Methods

A hospital-based cross-sectional study conducted at El Galaa Hospital in Tripoli city, from October to December 2024. Data collected using a 24-item questionnaire covering demographics, diagnosis history, dietary challenges, and neurodevelopmental outcomes. The data was analyzed using SPSS software.

Results

The study includes 24 patients diagnosed with PKU. Age distribution shows that 50% were aged 10-19, 41.7% aged 20-29, and 8.3% aged 30-39.

Table 1: Shows Percentage of PKU patients according to age

age groups	Frequency	Percentages
10-19 years	12	50%
20-29years	10	41.7%
30-39 years	2	8.3%
Total	24	100 %

Gender analysis revealed a higher prevalence among females (70.80%) compared to males (29.20%).

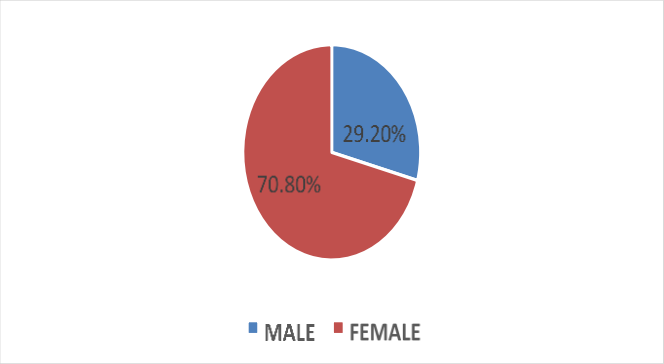

Figure 1: Distribution of PKU patients according to the gender

Place of residence varied, with the highest concentration in Gharyan (33.3%) and Tripoli (29.2%) and lowest in Al-Khums, Zuwara, Al-Zahraa (4.2% in each city).

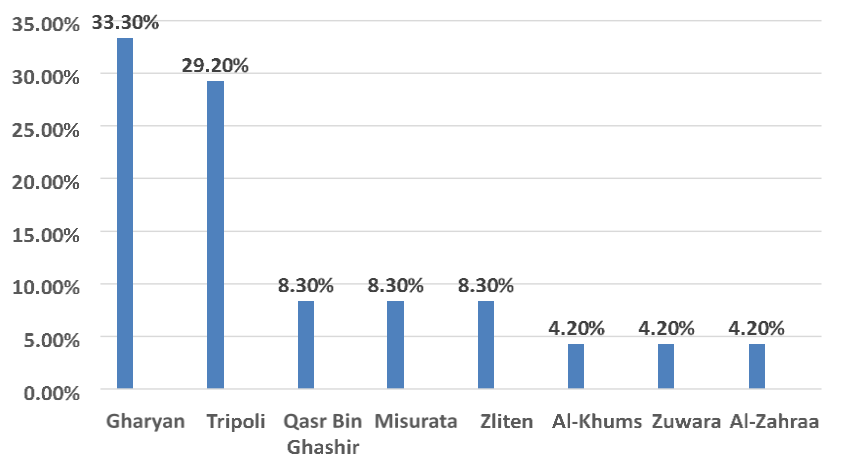

Figure 2: Distribution of PKU patients according to place of residence

Diagnosis history indicated that 37.5% were diagnosed after one year of age, while 33.3% were diagnosed at birth.

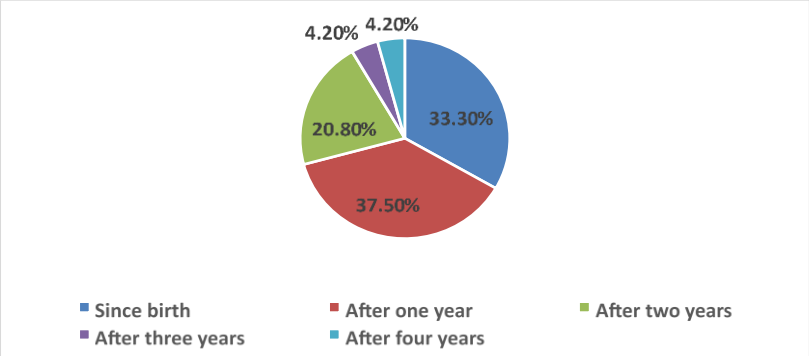

Figure 3: Diagnosishistory of PKU discovery

The results shows that 62.5% of the patient's families have two members affected , 25% only one member and 8.3% three members were affected while 4.20% there was no one affected except the patient.

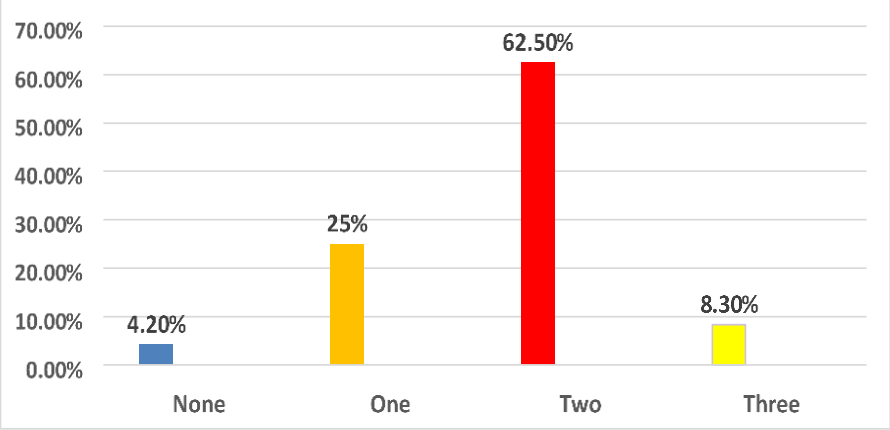

Figure 4: Number of affected patient's family members by PKU

And Genetic testing was performed for 95.8% of patients and 20.8% of parents, all patients under the study confirmed consanguinity among parents.

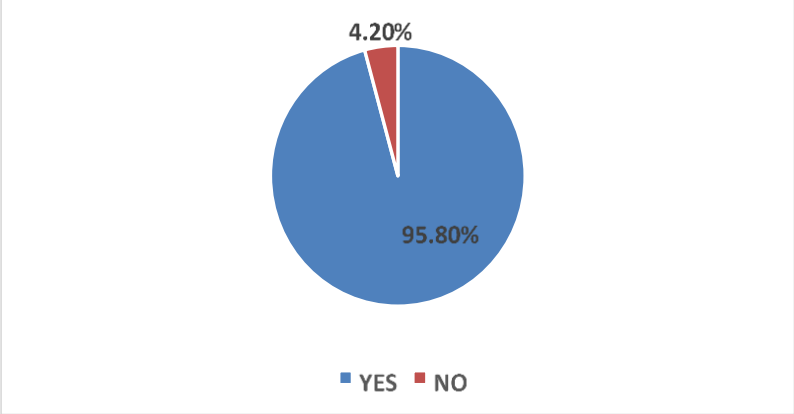

Figure 5: Percentage of genetic tests performed for PKU patients

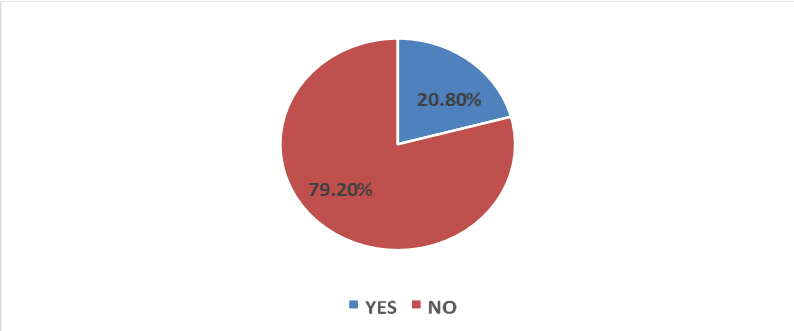

Figure 6: Percentage of genetic tests performed for PKU patient' parents

Regarding parental understanding to the nature of PKU, The highest percentage was understanding (79.2%), but 83.3% reported difficulties in adhering to the dietary regimen.

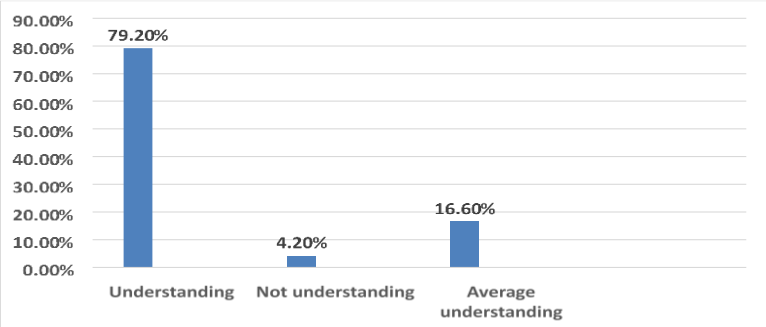

Figure 7: Percentage of Parents' Understanding the nature of PKU disease

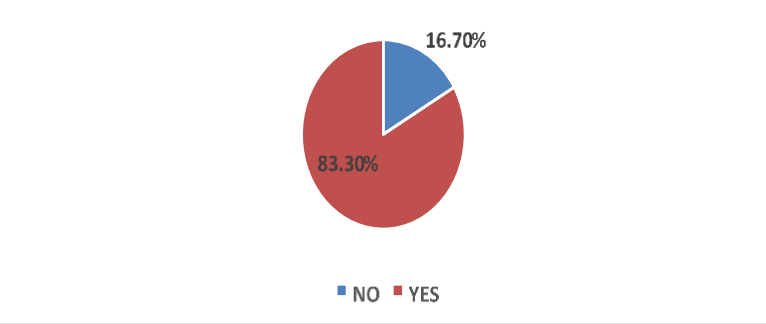

Figure 8: Distribution of families according to difficulties in adhering to the dietary regimen

In Figure 9 & 10 mental and behavioural complications were observed in 20.8% of patients and 25% experienced growth and developmental delays.

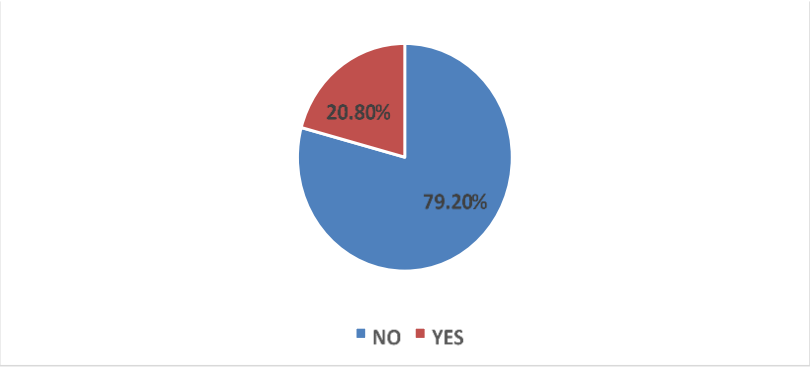

Figure 9: Distribution of PKU patients according to the occurrence of mental and behavioural complications

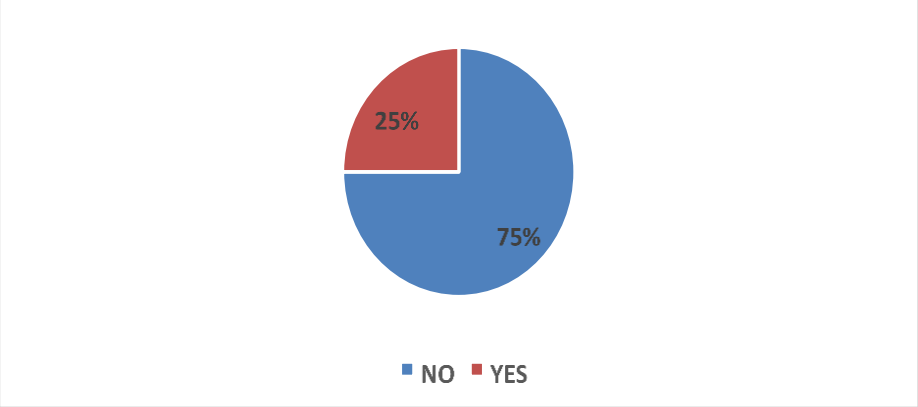

Figure 10: Distribution of PKU patients according to the occurrence of growth and developmental delays

Despite challenges, 75% of patients overcame the disease without complications, although 12.5% reported societal bullying as shown in figure 11&12.

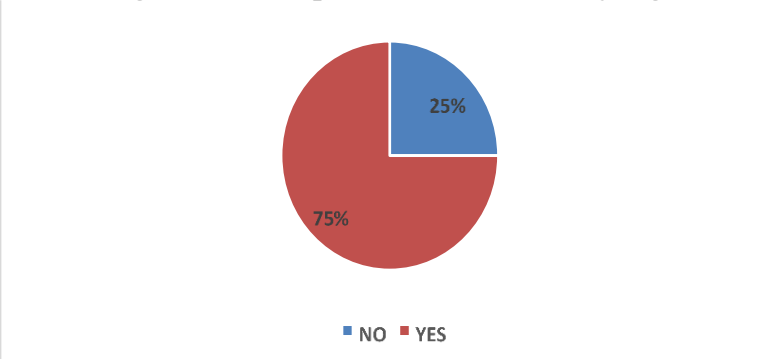

Figure 11: Distribution of PKU patients who survived without complications

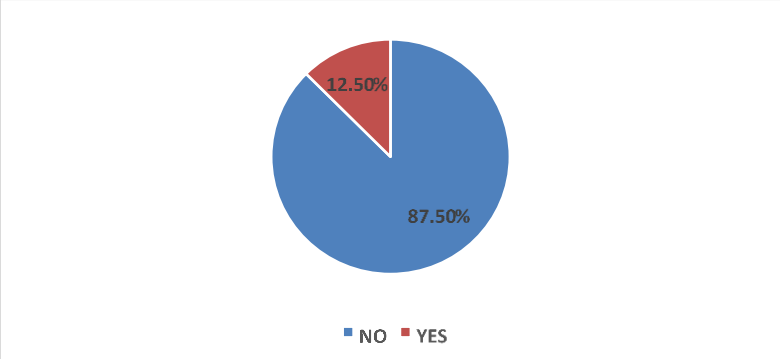

Figure 12: Distribution of PKU patients who suffer from bullying in the community

Discussion

Analysis of phenylketonuria (PKU) patients in our cohort based on age reveals a significant predominance of younger age groups, with half of them aged 10-19 years and 41.7% aged 20-29 years. Such a trend indicates that despite the delayed diagnoses, survival of patients into adulthood is high probably due to the long-lasting effect of dietary therapy. In this regard, the authors' findings are consistent with El-Moghrabi et al. (2014), who observed survival over time in PKU patients in Libya despite the limited healthcare system. The fact that late diagnoses still persist, however, points to the lack of a universally accessible newborn screening program which has been noted by El-Gharbi et al. (2010) that neonatal screening in Libya is economically viable.

Sex distribution in our research revealed a majority of females amongst the patients (70.8%), with males only making up 29.2%. In this respect, the study differs from worldwide registries like Hillert et al. (2020), which indicate almost equal sex ratios. The difference may be caused by gender-specific healthcare-seeking behaviors or sociocultural biases that lead to diagnosis and treatment of female children more than males. To investigate referral patterns and family attitudes, more qualitative research is needed as Anwar et al. (2014) stating that cultural norms play a significant role in prevalence of genetic diseases in North Africa.

With respect to location, most of the PKU patients were those from Gharyan (33.3%) and Tripoli (29.2%) as the data shows. Only a few of them came from rural areas. This urban concentration may simply reflect the referral patterns to the El Galaa Hospital and thus the prevalence of PKU in remote regions may be at the level that the data under represents. The World Health Organization (2025) has acknowledged that there are large differences in access to healthcare in Libya that border on the cause of the disparities. This, therefore, points to the necessity of locationally widespread screening and diagnostic services.

The proportion of patients diagnosed at birth was only one-third. Moreover, 37.5% of patients were diagnosed after the age of one year. These late diagnoses are of high clinical importance because van Spronsen et al. (2021) provided evidence that early diagnosis is the key to the prevention of cognitive impairment of irreversible nature. We are, therefore, a voice to a nationwide newborn screening program as Jafari et al. (2023) suggested. Their study in Iran found that neonatal screening led to better patient outcomes.

Consanguinity was reported in all cases of parents, and more than one affected member were present in 62.5% of families. These results are consistent with the regional data of Al Mutawa et al. (2010) and Khemir et al. (2012), which associate the high consanguinity rate with the elevated incidence of PKU. The genetic burden that can be seen calls for the introduction of premarital screening and genetic counseling programs, as Anwar et al. (2014) have pointed out and WHO public health recommendations have supported.

As a matter of fact, 95.8% of patients were subjected to genetic testing, while only 20.8% of parents did, thereby revealing a significant gap in cascade screening and carrier detection. This deficiency hampers the provision of personalized counseling and early intervention in the case of future pregnancies. Both Hillert et al. (2020) and Costa et al. (2020) highlight the significance of genetic testing of family members as a means of PKU management and risk reduction.

While 79.2% of parents correctly understood what PKU is, 83.3% of them reported that they had difficulty following the dietary regimen. The situation here goes beyond just educational gaps as it also shows the existence of economic and psychosocial barriers. Al-Arrayed et al. (2018) and the National Organization for Rare Disorders (n.d.) mention that the provision of medical foods free of charge, community support, and regular visits to a dietitian are very important to enhance adherence and end results.

Complications were only partially reported in 20.8% of individuals (mental/behavioral) and 25% (growth/developmental delays), while 12.5% of them were affected by bullying. Though 75% of patients managed to survive without any major complications, the issue of those who still have deficits due to late diagnosis and poor adherence is quite alarming. These results are similar to those of van Spronsen et al. (2021) who pointed out that the impact is lifelong and is caused by the failure of early management. The psychosocial burden brought by bullying and stigma, which are among the clinical challenges, also makes the situation worse and therefore, the need for targeted interventions.

Conclusion

The state of Phenylketonuria in Libya reflects the total absence of data in a high-risk regional and demographic situation. While there is no formally reported national prevalence, the high rates of consanguinity and an absence of hospital based studies indicate a substantial (but un quantified) public health burden due

to PKU and other IEMs .An important barrier for diagnosis and management is the collapsing health service infrastructure in Libya which leaves affected individuals and those around them with almost zero support. Our findings demonstrate the crucial value of early diagnosis and dietary management to counteract the effects associated with PKU. The high prevalence in females and psychosocial burden highlights a need for recommendations that focus on gender. Parental understanding and support are important to ensure adherence to dietary restrictions. Our study highlights the important role of genetic counselling as well as public awareness to reduce consanguineous marriages which are implicated in the incidence of PKU.

For PKU patients to have better neuro-developmental outcomes, early detection and intervention are crucial. To improve quality of life, comprehensive support networks are required, which include public education, psychological support, and dietary counselling. In high-risk groups, preventive measures like genetic screening and awareness campaigns can lower the prevalence of PKU.

Recommendations

- Expand newborn screening programs to ensure early diagnosis.
- Provide state-supported educational and psychological services.
- Develop adolescent-focused dietary adherence programs.
- Establish multidisciplinary care teams.
- Promote genetic counselling and premarital screening.
- Increase public awareness to prevent consanguineous marriages.

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