

Quality of Life and Psychological Distress in Women with Mayer-Rokitansky-Küster-Hauser Syndrome and Individuals with Complete Androgen Insensitivity Syndrome

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Abstract

Purpose: This study examines quality of life and psychological distress in individuals with Mayer-Rokitansky-Küster-Hauser Syndrome (MRKHS) and Complete Androgen Insensitivity Syndrome (CAIS), two syndromes belonging to the field of “disorders of sex development”. **Methods:** Fifty women with MRKHS and eleven individuals with CAIS participated. The German versions of the World Health Organization Quality of Life Questionnaire (short version, WHOQOL-Bref), the Brief Symptom Inventory (BSI), and the Patient Health Questionnaire (PHQ-D) were used as standardized instruments to measure quality of life and psychopathology. Additional questions concerning demographic variables and suicidality were included. **Results:** In both patient samples examined, general quality of life reported was in the average range (CAIS: mean z-score = -0.43, SD = 1.05; MRKHS: mean z-score = -0.11, SD = 1.06). The standardized instrument assessment revealed increased psychological distress (proportion of clinical cases according to the BSI: CAIS: 54.5%; MRKHS: 55.1%). A correlation between psychological distress and time span from first suspicion to diagnosis was found in women with MRKHS (Spearman’s rho = 0.35, p = 0.018). **Conclusions:** The results illustrate the importance of individualised and thorough diagnostics when dealing with patients with MRKHS or CAIS. Psychological distress might be an issue for these individuals and therefore should be considered in treatment and counselling.

Keywords

Mental Health, Quality of Life, Disorders of Sex Development (DSD),

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Mayer-Rokitansky-Küster-Hauser Syndrome (MRKHS), Complete Androgen Insensitivity Syndrome (CAIS)

1. Introduction

Mayer-Rokitansky-Küster-Hauser Syndrome (MRKHS) and Complete Androgen Insensitivity Syndrome (CAIS) are classified as “disorders of sex development” (DSD), and are further defined as “congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical” [1]. Due to this atypical development, at birth individuals with MRKHS and CAIS have an unremarkable female appearance and are raised as girls, but are unable to carry a pregnancy.

Approximately 1 in 5000 female births will be later diagnosed with MRKHS [2]. The diagnosis comprises the following criteria: 46, XX karyotype, complete or partial absence of a vagina and uterus, with otherwise typical female bodily development and functioning ovaries. Two predominating issues are described in the literature and are often the central focus of medical treatment: First, the inability to engage in vaginal intercourse without some form of treatment becomes problematic. Secondly, the realization that pregnancy will not be possible is an issue for affected individuals [3]. The majority of the medical literature has focused on treatments to create a so-called neovagina in order to allow sexual intercourse; various methods have been described, ranging from non-surgical approaches to different surgical procedures [4] [5].

A CAIS diagnosis has an estimated prevalence of 1 in 20 000 live births with 46, XY karyotype [6] [7]. Individuals have a 46, XY karyotype and undescended testes. Due to an insensitivity of the receptors in the target organs to testosterone, they are born with a female body appearance and either partially or completely lack a vagina and uterus. Nearly all published cases of individuals with CAIS report a female gender role [8] [9], while only 2 cases of a male gender identity have been described [10] [11]. Nevertheless, we have chosen gender-neutral terms (individuals/participants) when describing this group (members of the German self-help group pointed out that these terms feel more appropriate for some of the persons concerned). CAIS-diagnosed individuals may also be treated to create a neovagina.

Pre-pubertal development and the timing of diagnosis (often during puberty, because of primary amenorrhea) are similar in both conditions.

Systematic results reported for quality of life and psychological distress in these individuals are rare and often inconsistent between studies.

The World Health Organization defines quality of life as “individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” [12]. In this sense, it could be expected that MRKHS and CAIS both are conditions impairing quality of life, as they set limits to individual life goals and expectations (e.g. through the impossibility to carry a pregnancy), see also [13]. Systematic differences between these syndromes have remained poorly understood. Some studies find an impaired quality of life and higher psychological distress [3] [14] [15], others find no differences from non-clinical control samples [16] [17], and some studies even describe a better quality of life and less psychological problems compared to non-clinical samples [18]. Due to small sample size in previously published reports, the data on psychopathology reported should be considered preliminary [3] [15]. In some studies, individuals with CAIS have been included in larger samples with various other DSD diagnoses [19]. However, as the various DSD diagnoses are very heterogeneous, such results should not be generalized to the CAIS subgroup.

Correlations between psychological distress and the timing of diagnosis have been proposed, but again, the evidence seems to be inconsistent between studies. One study concluded that the later the condition is diagnosed, the better the ability of the patient to cope with the diagnosis [20]. Other authors assumed that an earlier diagnosis leads to better acceptance of the condition [21]. It was also hypothesized that the more years have passed since diagnosis, the better the acceptance of the condition [22].

Although the evidence on increased psychological distress does not seem to be without controversy, suicidal attempts in CAIS samples have been described for a proportion as high as 20% to 23% of study participants [14] [23].

Given the current paucity in data reporting quality of life and psychological distress in CAIS and MRKHS,

the purpose of the present study was to examine the impact of these diagnoses later in life and compare the two diagnostic groups with each other, and to non-clinical samples previously reported in the literature. Based on previously reported studies we hypothesized quality of life to be impaired in both groups, and psychological distress to be higher (associated with more psychiatric diagnoses and higher rates of suicidality in both groups compared to the non-clinical population). The degree of psychological distress was hypothesized to be increased in persons with certain characteristics (such as young age at diagnosis). Comparing the two groups, a greater impairment in psychological health was expected in people with CAIS based on the biological conditions. The karyotype is 46,XX in MRKHS (“female”) and 46, XY in CAIS (usually labelled “male”). Knowing about this incongruent genotype might intensify the feeling of being different in a person with CAIS who is experiencing herself as female and learns about her “male inside” at some point in life. Being different or rather “not normal” is one important issue often mentioned by afflicted individuals in connection with impaired mental health [24].

2. Method

2.1. Participants and Procedures

This study was part of a research project examining quality of life, hormone action, and femininity at the University Medical Center Hamburg-Eppendorf. 11 individuals with CAIS and 50 women with MRKHS were included in the analysis. Participants were contacted using several strategies in collaboration with the Tübingen University Hospital. Women with MRKHS who had undergone surgery at this hospital were contacted directly; furthermore, medical professionals (gynaecologists and endocrinologists) Germany-wide were provided with information letters, as was the German self-help group “Intersexuelle Menschen e.V.”. Finally, information about the study was distributed at scientific meetings, published in medical journals and via a website.

Written informed consent forms were obtained from all participants (minimum age for participation: 18 years). An expense allowance was distributed to study participants, aside from this no further incentives were available. This study was approved by the Ethics Committee of the relevant Medical Association.

All participants received a comprehensive questionnaire, which consisted of several standardized instruments, additional free questions, and space for supplementary notes. The questionnaire was either distributed via mail or could be filled out at the University Medical Center. Additional medical findings were included in the data analysis when provided by the participants or the attending physicians.

2.2. Instruments

The following standardized instruments were used to measure quality of life, psychological distress and psychopathology:

The World Health Organization Quality of Life (WHOQOL)-Bref, German version [25], a short version of the original WHO questionnaire, containing 26 items measuring the following broad domains: physical health, psychological health, social relationships, and environment.

The Brief Symptom Inventory (BSI), German version [26], contains 53 items, and was used to evaluate general psychological distress and nine subscales (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism).

The Patient Health Questionnaire, German version (PHQ-D) [27] was administered to capture the prevalence of specific psychopathological diagnoses and syndromes according to the DSM-IV [28]. It allows the assessment of threshold disorders (corresponding to specific DSM-IV diagnoses: major depressive disorder, panic disorder, bulimia nervosa) and subthreshold disorders (other depressive disorders, other anxiety disorders, probable alcohol abuse or dependence, somatoform and binge eating disorders) [29] [30]. The PHQ-D is supplemented by the open question “What is the most stressful thing in your life right now?”

Suicidal attempts were registered by the question “Have you ever tried to take your own life?” (yes/no).

2.3. Statistical Analysis

Results for the BSI and WHOQOL-Bref are reported as standardized values to allow comparison to the non-clinical population (T- and Z-scores were calculated using norm data for the German population provided by the test manuals [25] [26]).

Median values were chosen to describe additional age variables (first suspicion that something with their body

was different; diagnosis of CAIS or MRKHS, respectively; time span between first suspicion and diagnosis; and time passed since diagnosis).

For some topics (clinical relevance of BSI results; disorders according to the PHQ-D), percentages are reported. This is done despite the small sample size of the CAIS study group to illustrate trends in the data and to allow a first comparison of the two diagnostic groups. It has to be kept in mind that these are only tendencies (and no statistically significant results), and no evidence about population values can be concluded from this.

Group differences were calculated using Student t-tests or median tests; comparisons with control samples were conducted using 95% confidence intervals.

To assess the relationship between variables, Spearman's rank correlation coefficients (Spearman's rho) were calculated.

Missing data in the standardized instruments (BSI and WHOQOL-Bref) were replaced by individual mean subscale values (corresponding to the approaches described in the test manuals [25]). In cases with more than 25% of answers missing, participants were excluded from further analyses, and results are reported with reduced sample size.

An alpha level of 0.05 was used for all statistical tests.

3. Results

3.1. Sample Characteristics

Data from all 11 individuals with CAIS and 50 women with MRKHS could be analysed. In the CAIS group, 7 people became aware of the study via their self-help group, 1 via the Tübingen University Hospital, and 1 via the internet (2 via other means). In the MRKHS group, only 1 person was informed about the study by a self-help group, 25 individuals were enrolled via the Tübingen University Hospital, and 6 were informed via the internet. The remaining participants in the MRKHS group were either informed by their gynaecologist (3), by other physicians (2), other medical centers (1), other study participants (2) or did not answer this question (8).

Participants were eligible if they had been diagnosed with either CAIS or MRKHS. Confirmation of diagnosis was obtained in two steps. Questionnaire data were checked for diagnostic plausibility for all participants (this was considered second degree confirmation). For 5 of the participants with CAIS and for 30 of the participants with MRKHS the respective diagnosis was confirmed by the attending physician and/or medical records (first degree confirmation).

Mean age of individuals included in the CAIS group was 38.7 years (SD = 9.6) and in the MRKHS group 23.7 years (SD = 5.8). For all further age-related variables median values are reported in **Table 1**.

In the CAIS study group 6 participants lived in a relationship (5 with a male partner, 1 with a female partner), in the MRKHS study group 37 women reported having a relationship (all with a male partner). All study participants with CAIS were working (full or part-time) or in training, 5 study participants with MRKHS were unemployed, 45 women were working, in training or attending college.

All participants with CAIS had undergone gonadectomy, 2 had undergone additional surgery to create a neovagina. In the MRKHS study group 44 had undergone surgery, all to create a neovagina. Dilation was applied to create a neovagina without surgery in 2 participants with CAIS and in 2 participants with MRKHS.

3.2. Quality of Life

The WHOQOL-domain scores and the overall scores are reported in **Table 2**. Z-scores were calculated using age-adjusted comparison data for a German population sample [25]. The two diagnostic groups differed signifi-

Table 1. Age characteristics of CAIS and MRKHS study participants (in years).

Group	N	Age variables: Median (range)				
		Age ^a	Suspicion ^b	Diagnosis ^c	Time span 1 ^d	Time span 2 ^e
CAIS	11	39 (22 - 49)	13.5 (0 - 16.0)	16 (4 - 44)	4.5 (0 - 28.8)	15 (3 - 34)
MRKHS	50	22 (18 - 45)	15.5 (4 - 18.9)	16 (6 - 25)	0.1 (-8 ^f - 13) ^g	5 (0 - 29) ^g

^aAge = age at participation in the study; ^bSuspicion = age when it was first suspected (by the patient herself/the parents or other persons) that something with their body was different; ^cAge at diagnosis of CAIS or MRKHS, respectively; ^dTime span 1 = years passed between first suspicion and diagnosis; ^eTime span 2 = years passed since diagnosis; ^fIn one participant, the diagnosis was made 8 years before she noticed any differences concerning her body; ^gData from 47 participants with MRKHS; 3 participants had missing data.

Table 2. World Health Organization Quality of Life (WHOQOL)-Bref results.

WHOQOL-domain	CAIS (<i>N</i> = 11)		MRKHS (<i>N</i> = 49 ^c)	
	absolute value ^a		Z-score ^b	
	Mean (<i>SD</i>)	Mean _z (<i>SD</i> _z)	Mean (<i>SD</i>)	Mean _z (<i>SD</i> _z)
physical health	71.75 (18.24)	-0.65 (1.34)	79.56 (15.57)	-0.45 (1.14)
psychological health	54.24 (24.08)	-1.41 (1.62)	69.81 (18.55)	-0.56 (1.24)
social relationships	60.61 (20.78)	-0.72 (1.28)	72.79 (22.16)	-0.22 (1.27)
environment	73.30 (13.29)	0.16 (0.97)	77.34 (12.87)	0.47 (0.94)
overall	62.50 (18.54)	-0.43 (1.05)	73.21 (17.68)	-0.11 (1.06)

^aScores ranging from 0 - 100, according to the proposed transformation in the manual [25]; ^bData basis for Z-Transformation was a German population sample [25]; ^cReduced sample size because of missing data in one participant.

cantly in the domain of psychological health, with lower values in the CAIS sample (mean values: CAIS = 54.24; MRKHS = 69.81; $T = -2.38$, $df = 58$, $p = 0.021$). No differences emerged for the other domains as well as for the overall score.

According to Z-transformations, nearly all scores fell in the average range (z between -1 and 1) the only exception being psychological health in the CAIS group: Z-scores of -1.41 indicated psychological health below average for the CAIS sample.

3.3. Psychological Distress and Psychopathology

The Global Severity Index (GSI) of the BSI and the subscale scores could be calculated for 60 study participants. (One woman with MRKHS had to be excluded because of missing data.) T-values are reported in **Table 3**. No significant differences were found between the two diagnostic groups.

Individuals who reach a score of 63 or higher in the GSI or in two or more subscales are categorized as “clinical case” [26]. Using this classification, the means of both study groups were below the cut-off for clinical relevance. However, in both samples a considerable percentage of clinical cases were found (also shown in **Table 3**).

In the CAIS sample no significant correlations between age variables (**Table 1**) and general psychological distress emerged. In the MRKHS group significant relationships between general psychological distress and age at first suspicion were found (Spearman’s $\rho = -0.30$, $p = 0.035$), as well as between general psychological distress and time span from first suspicion to diagnosis (Spearman’s $\rho = 0.35$, $p = 0.018$).

Table 4 reports the results of the PHQ-D. Taking PHQ-D data from a German non-clinical female sample as a basis [31], the rate for major depressive disorder was more than twice as high in both study groups. Rates for other disorders were in the scope of results reported for primary care patients from an American sample [30].

When asked “What is the most stressful thing in your life right now?”, problems concerning job, career or school were mentioned most frequently in both groups (CAIS: 3 participants; MRKHS: 14 participants). Problems closely related to the diagnosis were reported by 2 participants in the CAIS sample (hormone replacement therapy) and 13 participants in the MRKHS sample (infertility/living with the diagnosis/consequences of surgery).

3.4. Suicidality

Suicidal attempts were reported by 2 persons in the CAIS sample and by 4 persons in the MRKHS sample. Considering confidence intervals, these prevalence rates were significantly higher than those found in a German non-clinical comparison sample [33] (lifetime suicide attempts: 1.7%; 95% CI 1.24 - 2.16; mean age for the German sample was not reported).

4. Discussion

4.1. Key Results

The Quality of life was in the average range for both the CAIS and MRKHS study participants. Corresponding

Table 3. Brief Symptom Inventory (BSI): Global Severity Index (GSI), subscale results (T-values^a) and clinical cases.

BSI results	CAIS (N = 11)		MRKHS (N = 49 ^b)	
	Mean	(SD)	Mean	(SD)
GSI	60.91	(10.30)	57.31	(14.01)
<i>Subscale results</i>				
Somatization	56.73	(11.16)	53.06	(10.61)
Obsessive-compulsive	59.36	(9.78)	54.14	(11.70)
Interpersonal sensitivity	61.64	(10.46)	57.86	(11.45)
Depression	60.36	(12.38)	55.67	(13.06)
Anxiety	57.27	(11.22)	53.67	(12.42)
Hostility	60.09	(11.20)	59.57	(10.73)
Phobic anxiety	56.64	(12.46)	54.12	(11.38)
Paranoid ideation	54.00	(11.14)	57.31	(11.40)
Psychoticism	59.91	(11.31)	56.57	(11.90)
<i>Clinical Cases^c</i>	<i>n</i>	<i>(%)</i>	<i>n</i>	<i>(%)</i>
	6	54,5%	27	55,1%

^amean = 50, standard deviation = 10; ^bBSI results could not be calculated for one participant with MRKHS because of missing data; ^cParticipants (number and percentage) whose individual scores exceed the criterion for clinical relevance; (GSI T-value ≥ 63 , or T-values ≥ 63 in two or more subscales).

Table 4. PHQ-D results for threshold and subthreshold disorders.

PHQ-D results	CAIS (N = 11)		MRKHS (N = 50)		Comparison data
	No.	(%) ^a	No.	(%)	
<i>Threshold disorders^b</i>					
Major depressive disorder	1	(9.1%)	6	(12.0%)	2.2% ^c
Panic disorder	--		--		2.8% ^d
Bulimia nervosa	1	(9.1%)	1	(2.0%)	1.0% ^e
<i>Subthreshold disorders^b</i>					
Other depressive disorder	1	(9.1%)	4	(8.0%)	2.5% ^c
Other anxiety disorder	1	(9.1%)	3	(6.0%)	7.0% ^e
Probable alcohol abuse	--		3	(6.0%)	7.0% ^e
Somatoform disorders	1	(9.1%)	3	(6.0%)	4.2% ^c
Binge eating disorders	1	(9.1%)	1	(2.0%)	6.0% ^e

^aPercentages are shown despite the small sample size to allow the comparison of tendencies in the two diagnostic groups. Please note that no; evidence about group differences can be concluded from this; ^bClassification according to descriptions in the German validation study [29]; ^cPrevalence rates in the German population, measured by the PHQ-9 and PHQ-15 [32]; ^dPrevalence rates of disorders according to the brief PHQ; rates for females [31]; ^ePrevalence rates detected by the PHQ in primary care patients [30].

to our first hypothesis, general psychological distress was increased in both study groups. Although GSI scores and BSI-subscale scores fell below the cut-off criterion for clinical relevance in both groups, a considerable percentage of individuals classified as “clinical cases” were found in both groups. In MRKHS, general psychological distress was higher the younger the women were when it was first suspected that something with their body was different, and when more time had passed between this first suspicion and diagnosis. Increased rates of major depressive episodes (as measured by the PHQ-D) and high suicidality further demonstrate that both groups suffer from impaired mental health. Lifetime suicide attempts lay within the range reported for individuals with mental disorders (e.g. major depressive episodes: 8.36%; panic disorder: 10% [33]). They were even slightly higher than the rates in a German sample of individuals with different forms of disorders of sex development (5.4%) [14], but were below the rates found for CAIS samples reported in two other studies from Ger-

many and America (20% and 23%) [14] [23].

In line with our second hypothesis, psychological health (as measured by the WHOQOL-Bref) was significantly lower in the CAIS sample. However, no significant differences emerged when comparing the other scores describing quality of life and mental health.

4.2. Limitations

The study has a number of limitations that have to be considered when interpreting the results. As the sample sizes between our study groups differ to such a great extent, unfortunately no robust conclusion can be drawn from the group comparisons.

Our proceeding to contact potential participants may have led to selected study samples. The MRKHS study group had only little age variance and the majority of participants in this group had been recruited via their physicians, most of them after they had undergone surgery to create a neovagina. Therefore, we may have examined only a special subgroup of women with MRKHS. The CAIS sample was partly recruited via self-help groups, which also may have led to a bias in the results. Unfortunately, the sample is too small to make comparisons between subgroups (e.g. individuals who joined a self-help group compared to those who did not).

When using norm data for the standardized instruments, groups that are comparable in age distribution are not always available, often only data for the general population are reported.

In the present study, only a limited number of variables have been examined. The main focus lay on the description of the results in the standardized instruments to provide further information for clinicians working with such patients, and as a basis for further research on these rare conditions.

4.3. Interpretation of Results

Our findings on quality of life correspond to results reported by other studies (e.g. for an Australian MRKHS cohort [16] and for a CAIS cohort in the United Kingdom [17] and are in line with the answers provided by the study participants when asked about the most stressful thing in their life. In both groups, the majority of participants experienced current problems concerning job/career/school as most stressful, all of which were unrelated to their diagnosis. Thus, it is plausible to argue that their diagnosis is not the driving force behind the most draining aspect of their daily lives and as such does not have a measurable impact on their quality of life. However, a substantial proportion of the study participants reported experiencing problems closely related to CAIS or MRKHS as most stressful (e.g. hormone replacement therapy in CAIS, infertility in MRKHS). Study participants with CAIS often mentioned psychological problems, going together with low WHOQOL scores for “psychological health” in this study group. This illustrates the importance of individualised and thorough clinical diagnostics when dealing with patients, as individual problems may be missed when only standardized instruments are used for screening.

The BSI scores provide more detailed information about psychological health. At first view, these data showed an average level of psychological distress in the CAIS and MRKHS study groups, corresponding to findings described in a clinical case report series on vaginal agenesis [34]. However, upon closer examination of the individually reported values, the data revealed that in both groups a considerable percentage of participants had to be classified as clinical cases. These participants reported psychological distress that has to be considered as clinically relevant. This is in line with previously published data from the Hamburg Intersex Study [14] and results reported for MRKHS [21] [35] [36].

These results demonstrate that different methods of analysing the data—using cut-off values, group comparisons or the definition of clinical cases—may lead to different conclusions. This may be one possible reason explaining some of the inconsistencies of results reported in the literature.

Psychological distress in the MRKHS study group was higher in women who were relatively younger at the time when it was first suspected that something with their body was different. This result is in line with the thought that the later a difference is detected, the better the coping, as the young women have had more time to form a “stable identity” [20]. In this context, a similar correlation between distress and age at diagnosis was expected. This, however, could not be found. Not the date of the medical diagnosis seems to be crucial, but the beginning of the individual feeling of difference from peers (which can be long before diagnosis but also at the same time) may go together with impaired psychological well-being. Although it seems plausible to expect the psychological impact of the diagnosis to decrease over time [22], no correlation between psychological distress

and years since diagnosis emerged. Heller-Boersma and colleagues described similar results [22]. Measuring distress in the months after diagnosis may be a more adequate way for analysing the expected correlation, merely looking at the years after diagnosis might be too crude.

An interesting finding that has not been described before is the positive correlation between psychological distress and the time span from first suspicion to medical diagnosis in MRKHS. This longer time span until diagnosis might go together with prolonged uncertainty about one's own condition. The concept of "uncertainty in illness", describing the inability to determine the meaning of illness-related events [37], has been described as potentially stressful. This may be an important factor influencing well-being in individuals with CAIS and MRKHS, as these conditions are relatively rare and thus the diagnostic process can take a long time. As no hypothesis had been formulated expecting this tendency, this finding is merely explorative. In the CAIS sample no such correlations were found, which may be due to smaller sample size in the CAIS study group.

We propose that looking at longer time spans might reveal no linear correlation between current age and distress but rather an increase and decrease of psychological distress over the lifecourse, as specific topics, e.g. infertility, become more salient in certain phases of life (as described in a qualitative study on vaginal agenesis by Holt & Slade [38]). To test this hypothesis, studies with larger samples and participants of different age groups are necessary.

4.4. Generalisability

Although the CAIS study group was quite large considering the rareness of the condition, it was too small to draw robust conclusion about the CAIS population. The results can only highlight tendencies and further research is needed, especially with regard to the group comparison between individuals with CAIS and MRKHS.

The MRKHS study group was rather homogenous (mostly young women after surgery). Therefore the results should not be generalized to other age groups or women who decided against surgery. In our study, as well as in the literature, systematic information about women who have not been treated surgically is lacking. Further studies are needed to learn more about this under-researched group.

4.5. Conclusion

In conclusion, this study found that psychological distress might be an issue for individuals with CAIS and MRKHS and therefore should be considered in treatment and counselling. It is known that group interventions can effectively reduce distress in individuals with MRKHS [39] [40]. This emphasizes the importance of identifying affected individuals and offering them adequate support.

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