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(REVIEW ARTICLE)

MRI changes of the pituitary gland and brain in Thalassemia major: A comprehensive review of clinical implications

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Abstract

Introduction: Thalassemia major is a genetic disorder characterized by chronic anemia requiring frequent blood transfusions, leading to iron overload in various organs, including the pituitary gland and brain. MRI is a pivotal tool in assessing the extent of iron deposition and its clinical consequences in these patients.

Objective: To summarize the MRI findings related to pituitary and brain changes in thalassemia major and to elucidate their clinical implications based on existing literature.

Methods: A comprehensive review of the literature was conducted, focusing on studies that employed MRI to investigate pituitary and brain changes in patients with thalassemia major. Data extracted from these studies included the number of patients, MRI findings, and associated clinical outcomes.

Results: The review included studies published between 1998 and 2022. Key findings are as follows:

Pituitary Gland Changes: Multiple studies reported reduced pituitary gland volume and signal intensity, correlating with hypogonadotropic hypogonadism (HH) and delayed puberty. Specific MRI metrics such as pituitary-to-fat signal intensity ratios (SIRs) and pituitary-R2 values were elevated in patients with HH, indicating significant iron overload.

Brain Changes: Increased brain T2* values indicative of iron overload was observed.

Clinical Associations: The MRI findings were consistently associated with various endocrinal abnormalities, including hypogonadism, short stature, delayed puberty, and growth hormone deficiency. Severe pituitary iron deposition and volume loss were predictive of hypogonadism. Specific studies highlighted the independent progression of iron overload in different organs, emphasizing the importance of organ-specific MRI evaluation.

Additional Findings: Notably, iron chelation therapy showed potential benefits in reversing some of the endocrinal and cardiac complications associated with iron overload.

Discussion and Conclusions: MRI is a valuable diagnostic tool for detecting iron overload in the pituitary gland and brain in thalassemia major patients. The findings from various studies highlight significant clinical implications,

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including hypogonadotropic hypogonadism, delayed puberty, and growth hormone deficiency. Regular MRI assessments, along with appropriate chelation therapy, are crucial in managing and mitigating these complications. Further research is needed to establish standardized MRI protocols and improve early diagnosis and treatment outcomes in thalassemia major.

Keywords: Iron overload; MRI; Cytotoxic effects; Pituitary size; Endocrine dysfunction; Iron chelation

1. Introduction

1.1. The Effect of Iron Overload on the Pituitary Size

Patients with thalassemia major frequently require repeated blood transfusions, which can lead to significant iron overload in various tissues, including the pituitary gland. This accumulation of iron within the pituitary gland can be effectively visualized and quantified using MRI techniques such as T2* relaxation time and pituitary R2 values. Studies have demonstrated that increased pituitary iron load correlates with reduced pituitary gland height and volume, which are observable on MRI scans (Hekmatnia et al., 2010),[1] (Bozdağ et al., 2018).[2]

1.2. The Cytotoxic Effect of Iron through Oxidative Injury on Endocrine Cells

Iron overload can induce cytotoxic effects through the generation of reactive oxygen species (ROS), leading to oxidative stress and damage to cellular structures. In the anterior pituitary, this oxidative injury affects various cell types, including gonadotrophs, somatotrophs, and corticotrophs. The resultant cell damage and death lead to a decrease in the size of the pituitary gland, as observed in MRI studies showing reduced pituitary height and volume in affected patients. This cellular damage contributes to the endocrine dysfunction seen in thalassemia major patients, manifesting as hormonal deficiencies and impaired gland function (Argyropoulou et al., 2003),[3] (Singer et al., 2021).[4]

1.3. The Possible Effect of Iron Deposition in the Pituitary on Hormonal Functions Including Growth, Puberty, and Fertility

Iron deposition in the pituitary gland can disrupt its normal function, leading to significant endocrine complications. Hypogonadotropic hypogonadism is a common consequence, characterized by delayed puberty and impaired fertility due to reduced secretion of gonadotropins (Argyropoulou et al., 2003),[3] (Noetzli et al., 2012) [4]. Additionally, growth hormone deficiency can result from iron toxicity affecting somatotroph cells in the anterior pituitary, contributing to growth retardation in affected children (Yılmaz et al., 2021) [5].

1.4. The Effect of Iron Chelation on the Reversal of the Lost Pituitary Endocrine Function and Growth

Iron chelation therapy, particularly with agents such as deferoxamine and deferiprone, has shown promise in reversing some of the endocrine dysfunctions associated with iron overload. Intensive chelation therapy has been associated with improvements in pituitary function and normalization of gland volume, which are critical for the restoration of hormonal balance and growth. Studies have reported cases where patients on combined chelation therapy showed significant improvements in growth parameters and endocrine functions, including resumption of normal puberty and fertility (Farmaki et al., 2010)[6], and (Singer et al., 2021) [7].

Objectives

The primary objective of this review is to summarize the MRI findings related to pituitary and brain changes in patients with thalassemia major and elucidate their clinical implications based on existing literature. Specifically, the review aims to:

- Assess the impact of iron overload on the size and function of the pituitary gland in thalassemia major patients.
- Investigate the relationship between iron deposition in the pituitary gland and various hormonal dysfunctions, including growth, puberty, and fertility.
- Evaluate the potential for iron chelation therapy to reverse endocrine dysfunctions and promote normal growth and development in these patients.
- Highlight the role of oxidative injury due to iron deposition in causing cytotoxic effects on endocrine cells.
- Provide a comprehensive overview of the clinical implications of these MRI findings to improve diagnosis, treatment, and management strategies for thalassemia major.

2. Methods

To achieve these objectives, a comprehensive literature review was conducted, focusing on studies that employed MRI to investigate pituitary and brain changes in patients with thalassemia major. The methodology involved the following steps: (Figure 1)

2.1. Literature Search

- Databases: PubMed, MEDLINE, Scopus, and Web of Science were searched for relevant articles.
- Keywords: "thalassemia major," "MRI," "pituitary gland," "brain changes," "iron overload," "endocrine dysfunction," "iron chelation therapy," and "oxidative injury."

2.2. Inclusion Criteria

- Studies published between 1998 and 2022.
- Research articles that included MRI assessments of the pituitary gland and brain in thalassemia major patients.
- Studies that reported clinical outcomes associated with MRI findings.

2.3. Data Extraction

- Information was extracted on the number of patients, MRI findings, and associated clinical outcomes.
- Key metrics such as pituitary-to-fat signal intensity ratios (SIRs), pituitary-R2 values, and brain T2* values were noted.
- Clinical associations including hypogonadism, short stature, delayed puberty, and growth hormone deficiency were recorded.

2.4. Analysis

- Summarization of MRI findings and their correlation with clinical outcomes.
- Assessment of the role of oxidative injury in causing cytotoxic effects on the pituitary gland and its implications for gland size and function.
- Evaluation of the effectiveness of iron chelation therapy in reversing MRI-detected changes and associated endocrine dysfunctions.

By systematically reviewing the existing literature, this paper aims to provide a detailed understanding of the impact of iron overload on the pituitary and brain in thalassemia major patients and inform clinical practices for better management of the condition.

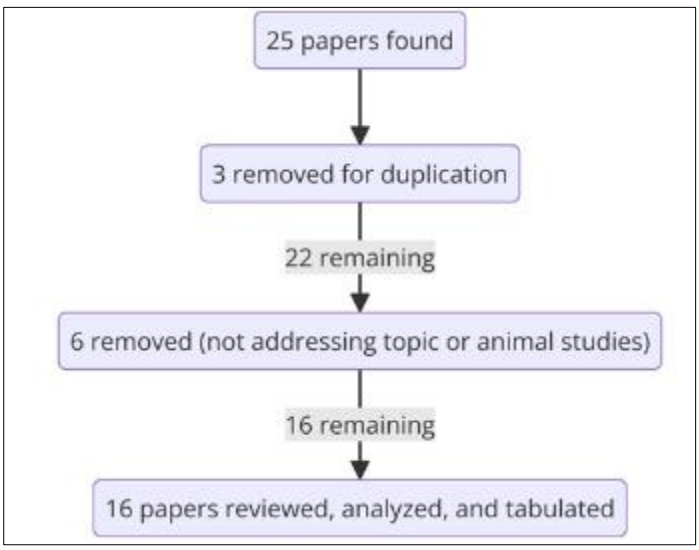

Figure 1 PRISMA Characteristics of the Review

3. Results

A comprehensive summary of the MRI findings and clinical associations in thalassemia major patients is presented in table 1.

Table 1 Summary of the MRI findings and clinical associations in thalassemia major patients

Author	Journal and Year	Number of Patients	MRI Findings Reported	Clinical Associations
K Y Lau et al.[8]	J Paediatr Child Health, 1998	12 children	No abnormal hypointense signal in hypothalamus or pituitary gland	No correlation with growth retardation
Maria I Argyropoulou et al.[3]	Eur Radiol, 2003	36 patients	Lower P/F ratio and pituitary T2 in hypogonadotropic hypogonadism group	Hypogonadotropic hypogonadism
Efthymia Alexopoulou et al.[9]	J Magn Reson Imaging, 2006	46 patients	Significant difference in liver and myocardium R2 values	Correlated with Gd DTPA concentration and liver iron concentration
Athanasios Christoforidis et al.[10]	J Pediatr Hematol Oncol, 2006	30 patients	No significant correlation between liver, pituitary, and cardiac MRI values	Independent progression of iron overload in different organs
Maria I. Argyropoulou and Loukas Astrakas [11]	Pediatr Radiol, 2007	Not specified	Increased iron deposition in the anterior pituitary gland, causing hypogonadotropic hypogonadism and growth hormone deficiency	Correlation between MRI indices and serum ferritin
Wing-Yan Au et al.[12]	Haematologica, 2008	180 patients	Significant correlations between organ iron assessments	Endocrine failures, heart failure predictions
Ali Hekmatnia et al.[13]	Acta Radiologica, 2010	27 patients	Lower pituitary-to-fat SIRs and reduced pituitary volume	Hypogonadism, delayed puberty
Leila J Noetzli et al.[4]	Am J Hematol, 2012	56 patients	Severe pituitary iron deposition and volume loss	Predictive of hypogonadism
Mustafa Bozdag et al. [2]	Acta Radiologica, 2018	38 patients	Higher pituitary-R2 values in HH group	Hypogonadotropic hypogonadism (HH)
SIK Karadag et al.[14]	Hemoglobin, 2020	50 patients	Moderate liver iron and mild pituitary iron	Hypogonadism, short stature
Sylvia T. Singer et al.[7]	Haematologica, 2021	53 patients	Moderate-severe pituitary iron deposition and gland shrinkage correlated with systemic iron load and reproductive dysfunction	Infertility issues, predictive markers for reproductive capacity
Kamil Yılmaz et al. [5]	Cureus, 2021	29 patients	No significant correlation with pituitary MRI T2* values	Low specificity for predicting short stature
N Dixit et al.[15]	Indian Journal of Pediatrics, 2021	50 patients	High prevalence of endocrinal abnormalities	Correlation with high serum TSH, blood sugars, delayed puberty
Jolyon Dales et al. [16]	Endocrine Abstracts, 2022	1 patient	MRI identified iron overload in the heart and liver; MRI pituitary showed loss of signal intensity in the anterior pituitary	Delayed puberty, growth hormone deficiency, hypogonadotrophic hypogonadism
Ashraf T. Soliman et al. [17]	J Trop Pediatr, 1999	17 patients	MRI studies revealed complete empty sella, marked diminution of the pituitary size, thinning of the	Defective GH secretion, growth retardation, and

			pituitary stalk, and evidence of iron deposition in the pituitary gland and midbrain	correlation with serum ferritin
J. Wood et al.[18]	Blood, 2012	31 patients	Pituitary R2 remained stable and pituitary volume improved over two years with deferasirox therapy	Reduced iron accumulation, gland shrinkage prevention, stabilized endocrine function

The table summarizes the MRI findings and clinical associations in patients with thalassemia major. Several studies consistently report significant iron deposition in the pituitary gland, leading to reduced gland volume and hypogonadotropic hypogonadism, as indicated by lower pituitary-to-fat signal intensity ratios (SIRs) and increased pituitary-R2 values [3, 4, 14]. These MRI findings are often associated with clinical manifestations such as delayed puberty, growth hormone deficiency, and short stature [1,3, 14]. Additionally, iron overload in other organs, like the liver and myocardium, is correlated with liver iron concentration and endocrine failures [9,12].

The review also highlights the variability in iron overload progression across different organs, underscoring the necessity of organ-specific MRI evaluations [7,10]. Iron chelation therapy has shown potential benefits in reversing some endocrine dysfunctions associated with iron overload, although its efficacy varies [3.15]. The correlations between MRI findings and clinical outcomes emphasize the critical role of regular MRI assessments in managing thalassemia major patients to mitigate complications and improve treatment strategies [11,15].

4. Discussion

The MRI findings of the pituitary gland in patients with thalassemia major varied significantly across different studies. Some studies found no abnormal hypointense signal in the hypothalamus or pituitary gland, while others reported lower pituitary-to-fat ratios (P/F) and pituitary T2 values, particularly in patients with hypogonadotropic hypogonadism. Significant differences in liver and myocardium R2 values were noted, though no significant correlations were found between liver, pituitary, and cardiac MRI values. Increased iron deposition in the anterior pituitary was associated with hypogonadotropic hypogonadism and growth hormone deficiency. Some studies reported severe pituitary iron deposition and volume loss, lower pituitary-to-fat signal intensity ratios (SIRs) and reduced pituitary volume. Higher pituitary-R2 values were observed in groups with hypogonadotropic hypogonadism. Moderate to severe pituitary iron deposition and gland shrinkage correlated with systemic iron load and reproductive dysfunction. However, no significant correlation was found with pituitary MRI T2* values in some studies. MRI findings also included iron overload in the heart and liver, loss of signal intensity in the anterior pituitary, complete empty sella, marked diminution of pituitary size, thinning of the pituitary stalk, and evidence of iron deposition in the midbrain. These MRI abnormalities were linked to endocrinological disorders, delayed puberty, growth hormone deficiency, and a high prevalence of endocrinal abnormalities. [2-18] (figure 2).

Figure 2: The images show varying degrees of pituitary abnormalities. Image (a) appears normal, while image (b) shows slight volume reduction and early iron deposition. Image (c) reveals marked anterior pituitary atrophy with iron deposition. Image (d) indicates severe atrophy and empty sella, Images (e) and (f) show severe atrophy of the anterior pituitary gland with iron deposition, leading to significant volume reduction and structural abnormalities. These findings are consistent with advanced pituitary damage due to iron overload, often seen in thalassemia major. (with permission from authors in reference [17])

The accumulation of iron in the pituitary gland leads to a decrease in gland volume and altered signal intensity ratios, which correlate with various endocrine dysfunctions. Hypogonadotropic hypogonadism (HH) and growth hormone deficiency (GHD) are among the most frequently reported complications, manifesting as delayed puberty and impaired growth [3.4,13]. These MRI-detected changes emphasize the importance of regular imaging in monitoring and managing the endocrine health of thalassemia major patients. In addition, there is MRI evidence supporting the effectiveness of iron chelation therapy in reducing iron deposition in the pituitary gland in thalassemia major patients. For example, a study found that pituitary R2 (a measure of iron) remained stable over two years in pediatric patients treated with deferasirox, and pituitary volume improved, suggesting that chelation therapy can prevent further iron accumulation and potentially reverse gland shrinkage. [18] Another study reported that pituitary-R2 values, measured using MRI, were significantly lower in patients undergoing chelation therapy, indicating reduced iron accumulation [2].

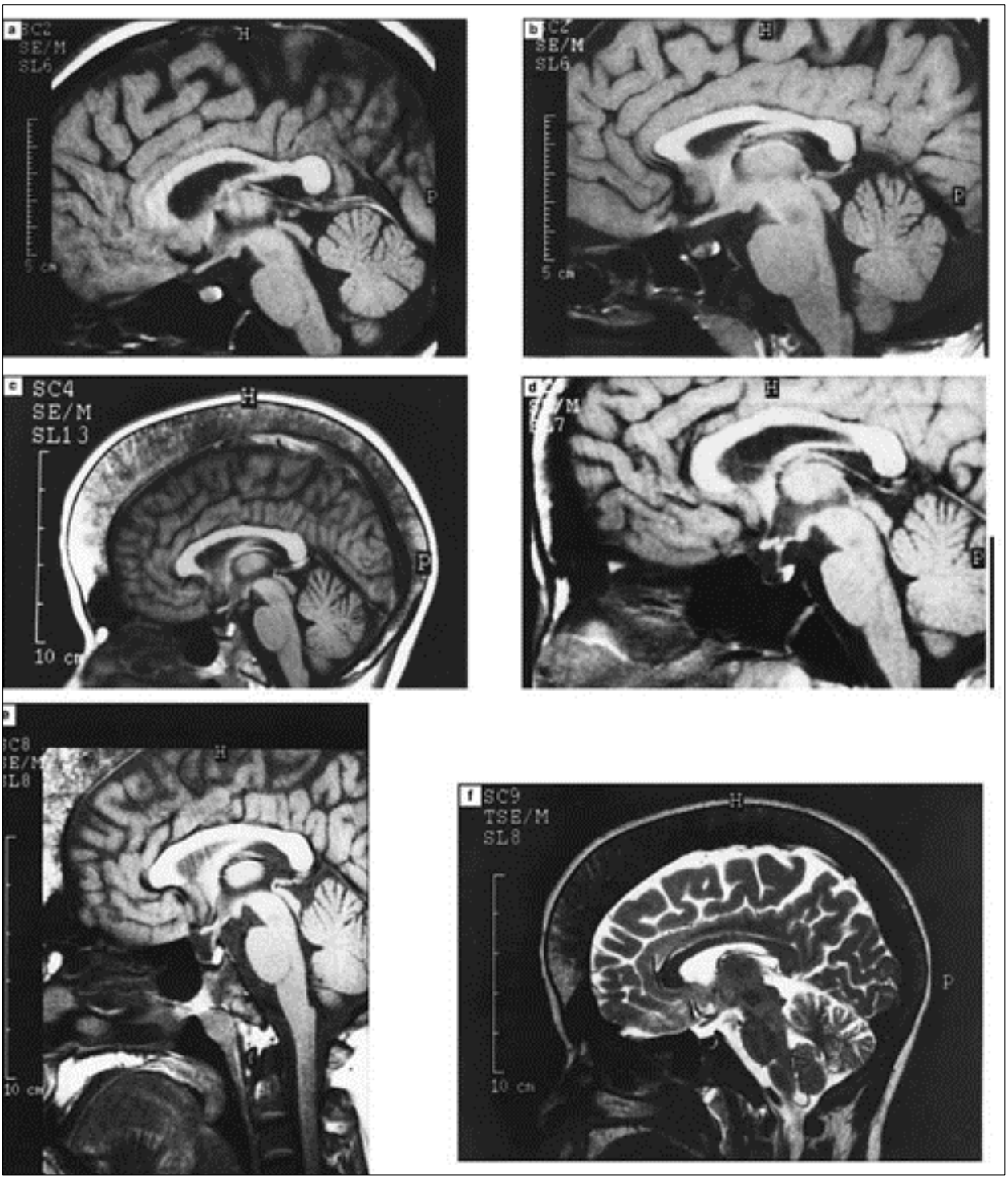

Figure 2 Different stages of pituitary involvement in Thalassemic patients

Iron deposition's cytotoxic effects are primarily mediated through oxidative injury, leading to cellular damage in the pituitary gland. The generation of reactive oxygen species (ROS) in response to iron overload results in oxidative stress, damaging the anterior pituitary cells, including gonadotrophs and somatotrophs. This damage contributes to reduced pituitary size and endocrine dysfunctions observed in patients [7,15]. Such oxidative injuries underscore the critical need for effective iron chelation therapies to mitigate these harmful effects and preserve pituitary function. (Figure 3).

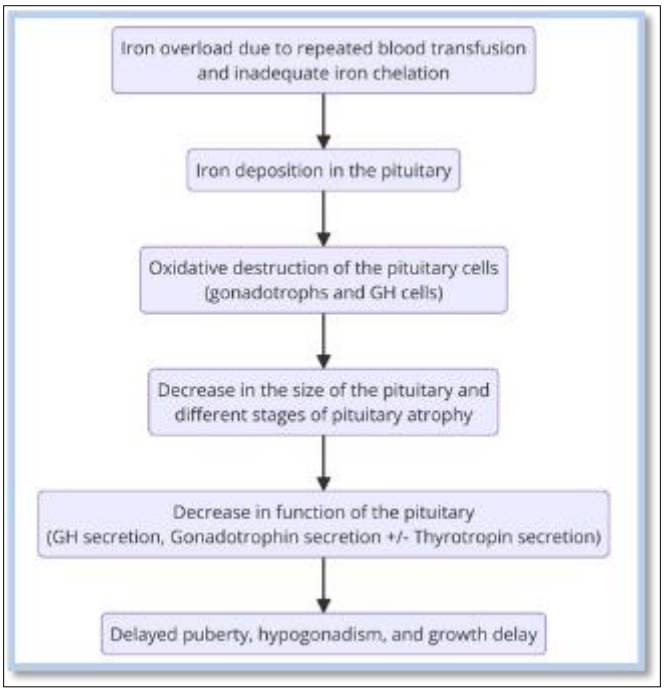

Figure 3 Proposed sequence of pathological events in the pituitary gland in patients with thalassemia major

The relationship between MRI findings and clinical outcomes is further corroborated by studies showing significant correlations between pituitary iron deposition and hypogonadism, as well as delayed puberty and short stature [3,4.14]. The variability in iron overload progression across different organs, as highlighted in this review, indicates that pituitary MRI assessments alone may not be sufficient. Comprehensive MRI evaluations of multiple organs, including the liver and myocardium, are essential to fully understand the extent of iron overload and its systemic effects [2,10,12].

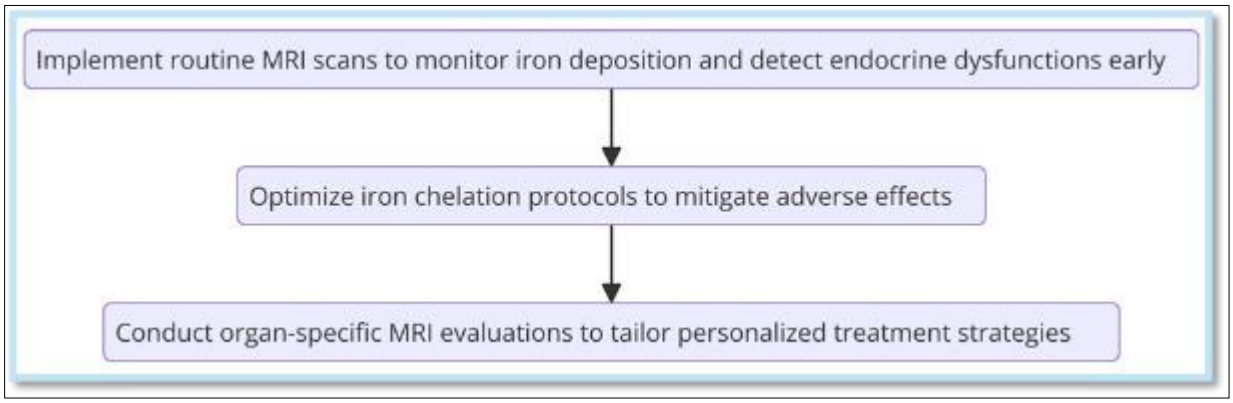

Figure 4 Recommendations on using MRI of the pituitary gland in patients with Thalassemia major

Iron chelation therapy has shown promise in reversing some of the endocrine dysfunctions associated with iron overload. Intensive chelation regimens using agents like deferoxamine and deferiprone have led to improvements in pituitary function and partial normalization of gland volume, which are crucial for restoring hormonal balance and promoting normal growth and development in patients [2,5]. These findings suggest that timely and effective chelation therapy can mitigate the adverse effects of iron overload and improve patient outcomes.

In conclusion, MRI is a valuable tool for detecting iron overload in the pituitary gland and other organs in thalassemia major patients. The clinical implications of these findings, including hypogonadotropic hypogonadism and growth hormone deficiency, highlight the necessity of regular MRI assessments and appropriate chelation therapy. Further research is needed to establish standardized MRI protocols and optimize treatment strategies to improve the long-term health and quality of life for patients with thalassemia major [7,11,16].

5. Conclusion

In patients with thalassemia major, iron overload from repeated blood transfusions significantly impacts the pituitary gland and other organs, as evidenced by MRI findings. The accumulation of iron leads to reduced pituitary volume and signal intensity, correlating with various endocrine dysfunctions such as hypogonadotropic hypogonadism, growth hormone deficiency, and delayed puberty. The cytotoxic effects of iron through oxidative injury contribute to cellular damage, further exacerbating these dysfunctions. Regular MRI assessments are crucial for detecting and monitoring iron overload in the pituitary gland and other organs, enabling timely intervention through effective iron chelation therapy. Intensive chelation therapy has shown promise in reversing some of the endocrine dysfunctions, highlighting the need for optimized treatment strategies to improve patient outcomes. Future research should focus on establishing standardized MRI protocols and exploring new therapeutic approaches to mitigate the adverse effects of iron overload in patients with thalassemia.

Recommendations: (figure 4)

- Implement routine MRI scans for thalassemia major patients with delayed puberty and/or growth delay to monitor iron deposition in the pituitary gland and other organs to detect and address endocrine dysfunctions early.
- Optimize iron chelation protocols, ensuring timely and intensive treatment to mitigate the adverse effects of iron overload on the endocrine system and improve patient outcomes.
- Conduct organ-specific MRI evaluations alongside standard pituitary assessments to understand the full extent of iron overload and tailor personalized treatment strategies accordingly.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict between the authors regarding the study. All authors have participated, reviewed and approved the publication of the study.

Author Contributions

AS was responsible for the conceptualization of the review study, setting the stage for the research with a clear outline of the scope and objectives. All authors actively participated in the data collection, screening, and analysis process, ensuring a comprehensive and meticulous evaluation of the research findings. The original draft preparation was undertaken by AS, who integrated the collected data and articulated the study's key insights. SB significantly contributed to reviewing the radiological MRI data and providing expert review and editing to enhance the intellectual content and clarity.

All authors have given their final approval of the version to be published, collectively ensuring the manuscript's accuracy and integrity, and have agreed to the published version, thus upholding rigorous scholarly standards, and ensuring the work's credibility and reliability.

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