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(REVIEW ARTICLE)

Effects of growth hormone and sex steroid therapy on brain structure and pituitary function in turner syndrome

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Abstract

Introduction: Turner syndrome (TS) is a chromosomal disorder affecting approximately 1 in 2,500 live female births, characterized by the partial or complete absence of one X chromosome. This genetic anomaly leads to physical, cognitive, and endocrine abnormalities, including short stature, gonadal dysgenesis, and structural brain anomalies. Cognitive deficits in TS involve visuospatial processing, memory, and executive function, often linked to structural brain changes. Magnetic resonance imaging (MRI) has revealed significant alterations in gray and white matter volumes in various brain regions. Growth hormone (GH) and sex steroid therapies, such as estrogen and progesterone, are used to address growth and developmental delays in TS. However, their impact on brain structure and pituitary function remains an area of active research.

Aim of the Review: To systematically review and synthesize findings on the effects of GH and sex steroid therapy on brain structure and pituitary function in patients with Turner syndrome.

Methods: A comprehensive literature review was conducted to identify studies examining the effects of GH and sex steroid therapy on brain structure and pituitary function in TS. Data from various sources were compiled, focusing on MRI-based structural brain changes. Key parameters analyzed included sample size, findings from MRI and fMRI studies, and clinical associations. Studies were summarized and presented in a structured table format.

Results: Estrogen-progesterone treatment was found to suppress pituitary gonadotropin release more effectively than estrogen alone, indicating a feedback interaction between pituitary gonadotropin release and sex steroids. MRI studies showed that TS patients exhibit smaller volumes in the hippocampus, caudate, lenticular, thalamic nuclei, and parieto-occipital brain matter, correlating with cognitive deficits. GH-IGF axis abnormalities are modulated by body composition and physical fitness, with sex hormone replacement normalizing the GH-IGF axis and improving body composition. Although GH therapy alone did not significantly improve cognitive functions, the combination of GH with oxandrolone improved working memory. Estrogen deficiency and TS are associated with slower growth in parieto-occipital regions and enhanced volume growth in basal ganglia and cerebellar areas during adolescence, underscoring the importance of estrogen replacement in brain development.

Discussion: GH and sex steroid therapies significantly impact brain structure, pituitary function, and clinical outcomes in TS. GH therapy, often combined with sex steroids, improves growth and cognitive functions, particularly working memory. However, GH alone does not significantly impact overall cognitive function. The timing and combination of these therapies are crucial for optimizing outcomes. Regular monitoring and individualized treatment plans are

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essential to address the complex needs of TS patients. Further research is needed to explore the long-term impacts of these therapies and develop optimal treatment regimens.

Conclusion: GH and sex steroid therapies are vital in managing TS contributing to improved growth, body composition, and cognitive enhancements. A multifaceted therapeutic approach and regular monitoring are crucial for optimizing treatment outcomes and quality of life for TS patients.

Keywords: Turner syndrome; Growth hormone therapy; Sex steroids; Brain structure; Pituitary function

1. Introduction

Turner syndrome (TS) is a chromosomal disorder affecting approximately 1 in 2,500 live female births. It is characterized by the partial or complete absence of one X chromosome, leading to a spectrum of physical, cognitive, and endocrine abnormalities. Patients with TS often exhibit short stature, gonadal dysgenesis, and various structural brain anomalies, which can result in cognitive impairments and social difficulties. Cognitive deficits frequently observed in TS include difficulties in visuospatial processing, memory, and executive function, which are believed to be associated with the underlying structural brain changes.

Magnetic resonance imaging (MRI) studies have provided valuable insights into the brain abnormalities associated with TS, revealing significant alterations in both gray and white matter volumes across different brain regions. These structural anomalies include reduced volumes in the hippocampus, amygdala, parietal, and occipital lobes, which correlate with the cognitive and neurodevelopmental challenges faced by individuals with TS (1), (2), (3).

Growth hormone (GH) and sex steroid therapies, such as estrogen and progesterone, are commonly employed to address the growth and developmental delays in TS. GH therapy is particularly effective in promoting linear growth, while sex steroid replacement helps in the development of secondary sexual characteristics and the maintenance of bone health. However, the impact of these therapies on brain structure and pituitary function remains an area of active research and clinical interest. Understanding the effects of these treatments is crucial for optimizing therapeutic strategies and improving the overall quality of life for individuals with TS (4), (5).

Aim of the Review

To systematically review the literature and synthesize findings on the effects of GH and sex steroid therapy on brain structure and pituitary function in patients with Turner syndrome.

2. Methods

A comprehensive literature review was conducted to identify studies examining the effects of GH and sex steroid therapy on brain structure and pituitary function in TS. Data from various sources were compiled, focusing on MRI-based structural brain changes. Key parameters analyzed included sample size, findings from MRI and fMRI studies, and clinical associations. Studies were summarized and presented in a structured table format.

3. Results

The following table and figure summarize findings from the reviewed studies:

Research on TS reveals significant insights into the cognitive, physical, and neurodevelopmental impacts of the condition. Cognitive deficits in TS patients are associated with smaller brain volumes in various regions, including the hippocampus, caudate, and thalamic nuclei, which correlate with visuospatial and memory impairments (2). Cognitive abilities are further influenced by the X chromosome and sex steroids, with mosaic TS individuals showing intermediate cognitive performance between those with full TS and healthy controls (3). Neuroendocrine studies indicate that body composition and physical fitness significantly modulate the growth hormone-insulin-like growth factor (GH-IGF) axis, which can be normalized with sex hormone replacement therapy, improving overall body composition and physical fitness (4). Estrogen-progesterone treatment effectively suppresses pituitary gonadotropin release, emphasizing the critical role of sex steroids in managing TS (1).

Table 1 Effect of GH and sex steroid therapy on the brain and pituitary functions in TS

Author	Year	Sample Size	Findings	Clinical Associations
Suetsugu N	1975	N/A	Estrogen-progesterone treatment suppresses pituitary gonadotropin release more effectively than estrogen alone	Feedback interaction between pituitary gonadotropin release and sex steroids (1)
Murphy et al.	1993	18 TS, 19 HC	Smaller hippocampus, caudate, lenticular, thalamic nuclei, parieto-occipital brain matter volumes	Cognitive deficits in visuospatial construction and memory correlated with karyotype (2)
Murphy et al.	1994	18 TS, 19 HC	Lower scores in language, visual-spatial function, attention, and memory; greater discrepancy in verbal vs. performance scores	Cognitive abilities affected by X chromosome and sex steroids; mosaic TS intermediate between full TS and controls (3)
Gravholt et al.	1997	27 TS, 24 HC	GH-IGF axis normal in TS; body composition and physical fitness modulate GH-IGF axis	Sex hormone replacement normalizes GH-IGF axis, improves body composition and physical fitness (4)
Gravholt et al.	1997	27 TS, 24 HC	GH-IGF axis normal, body composition and fitness key determinants, sex hormone replacement improves function	Body composition and fitness modulate GH-IGF axis in TS; sex hormone replacement normalizes GH secretion (4)
Ross et al.	1997	N/A	No effect of GH on cognitive function in TS	GH treatment does not influence neurocognitive outcomes in TS (5)
Balducci et al.	1998	9 TS	GH increases adrenal steroid responsiveness to ACTH	Potential modulation of adrenal enzyme activities by GH (6)
Gravholt et al.	1998	21 TS	GH secretion irregular, reduced mass and production rate in TS; body composition impacts GH secretion	Lean body mass and maximal oxygen uptake key determinants of GH secretion; sex hormone therapy improves GH levels (7)
Haeusler et al.	1996	20 TS	GH combined with oxandrolone improves final height; estrogen therapy delayed to enhance height gain	Combination therapy effective in increasing final height (8)
Ross et al.	2003	64 TS	Oxandrolone improves working memory in TS	Significant improvement in working memory with minimal side effects (9)
Cutter et al.	2006	27 TS, 21 HC	Smaller parieto-occipital cortex, caudate nucleus; increased hippocampal choline	X chromosome, imprinting, and neuroendocrine milieu modulate brain development (10)
Hampl et al.	2001	65 TS	SHBG levels normal or lower, significantly reduced with GH treatment	SHBG as a marker of response to GH administration (11)
Gravholt et al.	2002	12 TS, 16 HC	GH treatment reduces fat mass, improves lean body mass; impacts insulin sensitivity	Monitoring glucose metabolism essential during GH therapy in TS (12)
Li et al.	2019	23 TS	Estrogen deficiency affects gray and white matter development during adolescence	Highlights importance of estrogen replacement therapy for brain development in TS (13)
O'Donoghue et al.	2019	55 TS, 53 HC	Parieto-occipital gray and white matter regions showed slower growth during	TS girls may be particularly vulnerable to altered brain

			typical pubertal timing in girls with TS relative to typically developing girls. Enhanced volume growth in basal ganglia, cerebellar, and limited cortical areas	development during adolescence. Some basal ganglia, cerebellar, and limited cortical areas show enhanced volume growth with peaks around 10 years of age (14)
Lozano Wun et al.	2023	61 TS, 55 HC	Smaller total surface area and larger average cortical thickness overall. Regionally decreased volume and surface area in the pericalcarine, postcentral, and parietal regions. Larger volume in caudate, amygdala, and temporal lobe regions and increased thickness in parietal and temporal regions.	The results suggest the involvement of both direct and indirect effects of X-chromosome haploinsufficiency on brain development in TS (15).
Scheithauer et al.	2005	4 cases	"Gonadal failure cells" without recognizable gonadotroph hyperplasia, silent corticotroph microadenomas	Possible etiologic associations between Turner syndrome and pituitary adenomas (16)
Akkuş et al.	2023	35 TS, 20 HC	Pituitary hyperplasia in patients with inadequate hormone replacement therapy	Inadequate hormone replacement therapy can disrupt pituitary structure (17)
Samaan et al.	1979	7 TS, 3 Klinefelter's	Localized change in the sellar contour suggesting hyperplasia or microadenoma formation	Hyperplasia or microadenoma formation secondary to gonadal failure (18)

HC = healthy controls

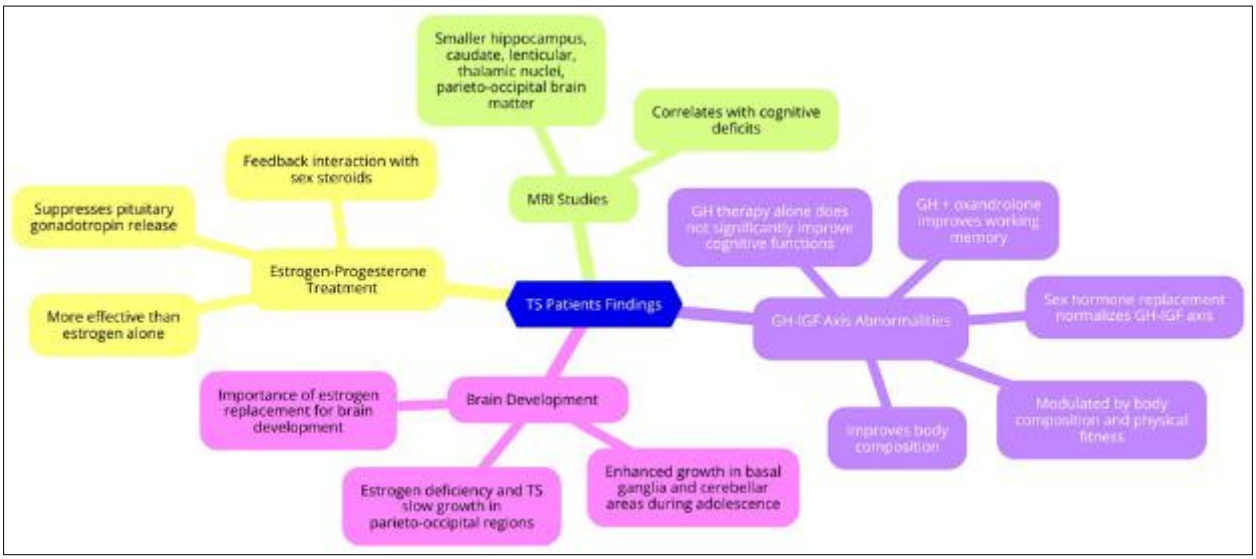

Figure 1 Effect of GH and sex steroid therapy on the brain and pituitary functions in TS

The impact of GH treatment on TS has been extensively studied. While GH does not appear to affect cognitive function (5), it does improve adrenal steroid responsiveness and body composition, particularly lean body mass and maximal oxygen uptake (6, 7). GH combined with oxandrolone significantly enhances final height and improves working memory with minimal side effects (8, 9). However, monitoring glucose metabolism is essential during GH therapy due to its effects on insulin sensitivity (12). Furthermore, estrogen deficiency during adolescence adversely affects brain development, underscoring the importance of estrogen replacement therapy for optimal neurodevelopment in TS (13). Alterations in brain structure, including reduced cortical surface area and increased cortical thickness in specific regions, suggest both direct and indirect effects of X-chromosome haploinsufficiency on brain development (15). This comprehensive body of research highlights the multifaceted nature of TS and the critical role of hormone therapies in mitigating its impacts.

4. Discussion

The reviewed studies consistently demonstrate that TS is associated with significant MRI changes in both brain and pituitary structures. The most common findings include reduced brain volume, particularly in the parietal and occipital lobes, and abnormalities in the hippocampus and amygdala, which are linked to cognitive deficits such as impaired visuospatial skills, memory, and social cognition (1), (2), (3). These cognitive impairments are often exacerbated by the structural anomalies identified in MRI studies, including reduced volumes in specific brain regions.

Growth hormone (GH) and sex steroid therapies have shown significant effects on brain structure, pituitary function, and clinical outcomes in TS. GH therapy, often combined with sex steroids, has been found to improve growth and some cognitive functions, particularly working memory. However, the evidence suggests that GH alone does not significantly impact overall cognitive function (4), (5). The normalization of the GH-IGF axis and improvements in body composition observed in some studies highlight the potential benefits of these therapies for physical development (6), (7).

Sex hormone replacement, specifically estrogen and progesterone, plays a crucial role in normalizing the GH-IGF axis, improving body composition, and enhancing physical fitness in TS patients. The combination of GH with oxandrolone, an anabolic steroid, has also been shown to significantly improve final height and cognitive functions such as working memory (8), (9). Despite these benefits, there are potential risks associated with GH and sex steroid therapies. These findings suggest that a multifaceted therapeutic approach is necessary to address the complex needs of individuals with TS.

Some studies have reported no significant cognitive improvements with GH therapy alone, emphasizing the need for combined therapeutic strategies (5). Additionally, the long-term impacts of these treatments on brain development and overall health outcomes remain unclear, necessitating further research and long-term studies (10), (11).

Regular monitoring and individualized treatment plans are essential to optimize therapeutic outcomes for patients with TS. Comprehensive neuropsychological and endocrine assessments should be conducted to address the multifaceted challenges faced by these individuals. Future research should focus on the long-term effects of GH and sex steroid therapies, exploring optimal treatment regimens that maximize both physical and cognitive development in TS patients (12), (13).

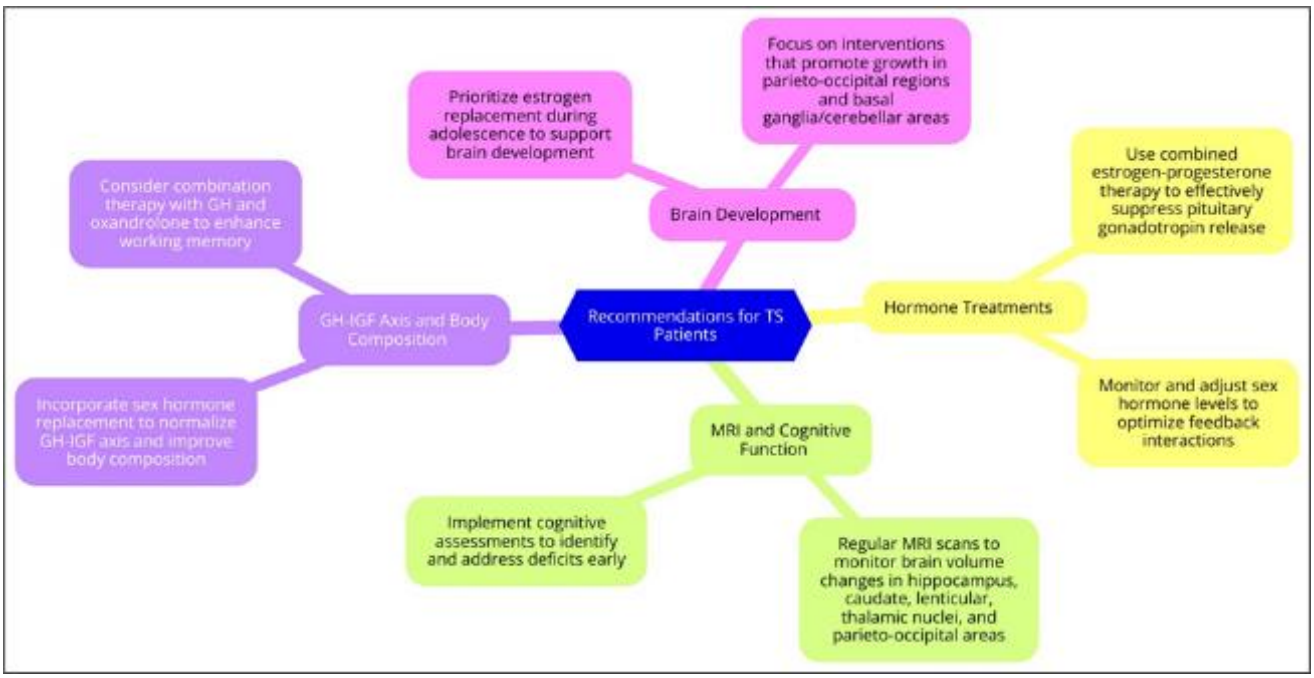

Figure 2 Recommendations based on the review results

5. Conclusions

GH and sex steroid therapies play a critical role in managing Turner syndrome. These therapies contribute to improved growth, better body composition, and certain cognitive enhancements, particularly in areas such as working memory. However, GH therapy alone does not appear to significantly influence overall cognitive function. The timing, combination, and individualization of these treatments are crucial for optimizing outcomes.

The reviewed studies highlight the need for a multifaceted therapeutic approach to address the complex needs of individuals with TS. Regular monitoring and comprehensive assessments are essential to tailor treatment plans that effectively address both the physical and cognitive challenges associated with TS. Further research is needed to explore the long-term impacts of these therapies and to develop optimal treatment regimens that maximize quality of life for patients with Turner syndrome.

Recommendations: Figure 2

- Combining GH therapy with sex steroids may enhance growth and cognitive functions, particularly working memory.
- Further research is needed to explore the long-term impacts of these therapies on brain cognitive and motor functions and develop optimal treatment regimens for TS patients.

5.1. Strengths

- The review systematically synthesizes a wide range of studies, providing a thorough overview of the effects of GH and sex steroid therapies on brain structure and pituitary function in Turner syndrome. This comprehensive approach ensures that multiple aspects of the condition and treatments are considered.
- **Clinical Relevance:** The findings highlight crucial therapeutic strategies that can directly improve patient cognitive and motor outcomes.

5.2. Weaknesses

Limited Long-term Data: The review indicates a need for further research on the long-term impacts of GH and sex steroid therapies. Current evidence may be insufficient to fully understand the prolonged effects of these treatments.

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. FA and AK significantly contributed to refining the manuscript, providing expert review and editing to enhance 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.

References

[1] Suetsugu N. The feedback effects of sex steroid hormones on pituitary gonadotropin release in Turner's syndrome and Klinefelter's syndrome. Endocrinologia Japonica. 1975; 22:111-121. doi:10.1507/ENDOCRJ1954.22.111.

[2] Murphy D, Decarli C, Daly E, et al. X-chromosome effects on female brain: a magnetic resonance imaging study of Turner's syndrome. The Lancet. 1993;342(8881):1197-1200. doi:10.1016/0140-6736(93)92184-U.

[3] Murphy D, Allen G, Haxby J, et al. The effects of sex steroids, and the X chromosome, on female brain function: A study of the neuropsychology of adult Turner syndrome. Neuropsychologia. 1994;32(10):1309-1323. doi:10.1016/0028-3932(94)00065-4.

[4] Gravholt CH, Naeraa RW, Fisker S, Christiansen JS. Body composition and physical fitness are major determinants of the growth hormone-insulin-like growth factor axis aberrations in adult Turner's syndrome, with important modulations by treatment with 17β-estradiol. The Journal of Clinical Endocrinology & Metabolism. 1997;82(8):2570-2577. doi:10.1210/jcem.82.8.4127.

[5] Ross JL, Feuillan P, Kushner H, Roeltgen D, Cutler GB Jr. Absence of growth hormone effects on cognitive function in girls with Turner syndrome. The Journal of Clinical Endocrinology & Metabolism. 1997;82(6):1814-1817. doi:10.1210/jcem.82.6.3945.

[6] Balducci R, Toscano V, Larizza D, et al. Effects of long-term growth hormone therapy on adrenal steroidogenesis in Turner syndrome. Hormone Research in Paediatrics. 1998;49(5):210-215. doi:10.1159/000023173.

[7] Gravholt CH, Naeraa RW, Fisker S, Christiansen JS. Lean body mass and maximal oxygen uptake are major determinants of growth hormone secretion in adult Turner syndrome. Clinical Endocrinology (Oxf). 1998;48(5):527-533. doi:10.1046/j.1365-2265.1998.00447.x.

[8] Haeusler G, Schmitt K, Blümel P, et al. Growth hormone in combination with anabolic steroids in patients with Turner syndrome: effect on bone maturation and final height. Acta Paediatrica. 1996;85(12):1408-1414. doi:10.1111/j.1651-2227. 1996.tb18382.x.

[9] Ross JL, Roeltgen D, Stefanatos G, et al. Oxandrolone in Turner syndrome: cognitive and behavioral features. The Journal of Pediatrics. 2003;143(5):653-658. doi:10.1067/s0022-3476(03)00557-5.

[10] Cutter WJ, Daly EM, Robertson DM, et al. Influence of X chromosome and hormones on human brain development: A magnetic resonance imaging and proton magnetic resonance spectroscopy study of Turner syndrome. Biological Psychiatry. 2006;59(3):273-283. doi: 10.1016/j.biopsych.2005.06.035.

[11] Hampl R, Hill M, Bicikova M, et al. Low SHBG concentrations in patients with Turner syndrome and the effect of GH treatment. Clinical Endocrinology (Oxf). 2001;54(4):497-502. doi:10.1046/j.1365-2265.2001.01236.x.

[12] Gravholt CH, Naeraa RW, Nyholm B, et al. Glucose metabolism, lipid metabolism, and cardiovascular function in adult Turner's syndrome. The impact of sex hormone replacement and growth hormone treatment. Clinical Endocrinology (Oxf). 2002;57(2):139-148. doi:10.1046/j.1365-2265.2002. 01572.x.

[13] Li M, Zhao C, Xie S, et al. Effects of hypogonadism on brain development during adolescence in girls with Turner syndrome. Human Brain Mapping. 2019;40(17):4901-4911. doi:10.1002/hbm.24745.

[14] O'Donoghue S, Green T, Ross JL, et al. Brain development in school-age and adolescent girls: Effects of Turner syndrome, estrogen therapy, and genomic imprinting. Biological Psychiatry. 2019;86(11):908-917. doi:10.1016/j.biopsych.2019.07.032.

[15] Lozano Wun V, Foland-Ross LC, Jo B, et al. Adolescent brain development in girls with Turner syndrome. Human Brain Mapping. 2023;44(10):4028-4039. doi:10.1002/hbm.26327.

[16] Scheithauer BW, Kovacs K, Horváth É, Young WF, Lloyd RV. The pituitary in Turner syndrome. Endocr Pathol. 2005;16(3):195-199. doi:10.1385/EP:16:3:195.

[17] Akkuş G, Kolsuz İ, Sozutok S, et al. Inadequate gonadal replacement in patients with Turner syndrome may result in pituitary volume enlargement. Curr Med Imaging. 2023. doi:10.2174/1573405619666230223170130.

[18] Samaan NA, Stepanas A, Danziger J, Trujillo J. Reactive pituitary abnormalities in patients with Klinefelter's and Turner's syndromes. Arch Intern Med. 1979;139(2):198-201. doi:10.1001/archinte.1979.03630390050021.