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## CHARACTERISTICS OF PATIENTS WITH GENERALIZED ANXIETY DISORDER IN HYPERTHYROIDISM ACCOMPANIED BY TONSILLITIS AND THYROID EYE DISEASE WITH ECG IMAGES OF SICK SINUS SYNDROME (SSS) IN CHILDREN AND ADULTS

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### KEYWORDS

hyperthyroid, generalized anxiety disorder, sick sinus syndrome, thyroid eye disease.

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### ABSTRACT

Hyperthyroidism is an endocrine disorder with the second-highest incidence rate after diabetes. Graves' disease is the most common cause of hyperthyroidism. Approximately 60% -80% of cases of hyperthyroidism are caused by Graves' disease, where women aged 20-50 are more dominant than men. Hyperthyroidism causes decreased heart rate and features an EKG pattern suggestive of sick sinus syndrome, including sinus bradycardia (heart rate <40 bpm), sinus pauses (sudden pauses in sinus nodes shorter than 2-3 seconds), and sinus arrest (sudden pauses in the sinus nodes). Sinus node longer than 2-3 seconds). This study aimed to determine the characteristics of patients with generalized anxiety disorder in hyperthyroidism accompanied by tonsillitis and thyroid eye disease with ECG features of sick sinus syndrome (SSS) in children and adults. This research uses the Systematic Review method using the preferred reporting items for systematic reviews and meta-analyses method, or PRISMA; this method is carried out systematically by following the correct research steps or protocols. Sources were taken from the PubMed site, and the Google Scholar site with journals published in 2017-2022 and then a screening was carried out to obtain 15,486 results. Based on the study's results, it was stated that journal clustering was carried out. The number of Scopus Q1 indexed journals was two journals, two journals Q2, and one journal indexed Sinta S1, so there were five extracted journals. It can be concluded that most journals discuss age and lifestyle related to the characteristics of the occurrence of panic disorders. The factors for hyperthyroidism are determined based on age and hyperthyroidism associated with panic disorders, an EKG picture of sick nodus dysfunction.

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## INTRODUCTION

Panic disorders can be interpreted as a feeling of fear, both of objects that are real or not, followed by an increased psychological reaction (Zaini, 2019). Other experts say that panic disorder is a form of unpleasant emotion characterized by worry, concern, and fear due to conflict, frustration, or pressure to do something beyond one's ability (Fukao et al., 2020) ; (Aizawa et al., 2018). Panic disorder has symptoms or signs that vary and differ from person to person. The degree of severity also varies from

person to person. Some of the symptoms that usually appear include feeling worried, having a bad feeling, irritability, feeling tense, uneasy, restlessness, sleep disturbances, such as difficulty sleeping, frequent nightmares, and other physical complaints such as muscle pain or shortness of breath. Research conducted on patients with Graves' disease showed that 41.67% of the subjects experienced anxiety with symptoms of insomnia, irritability, sadness, low self-confidence, and uneasiness. The manifestations of symptoms of psychological disorders experienced by these patients were also higher when compared to the control group (Azizi & Malboosbaf, 2017) ; (Kahaly et al., 2018) ; (Juwita et al., 2018).

The impact of panic disorder is related to the symptoms experienced. Panic disorder elicits a physical and psychological response. Physical response, for example, the heart beats faster, breaks out in cold sweat, breathes faster or is short of breath. This condition will make sufferers feel tired more quickly. Sufferers experience a change in their sleep patterns, making sleeping difficult, often having nightmares, or becoming sleepy quickly. This will also result in disrupted work productivity and physical disturbances (Huang et al., 2021) ; (Subekti & Pramono, 2018). If the anxious condition lasts for a long time, the sufferer will feel increasingly depressed, feeling uncomfortable in all situations. The result is that it can interfere with life and daily activities. The anxiety experienced by women who are mothers will also impact their family members. Mothers with high anxiety levels show a decrease in warmth, responsibility, and sensitivity in caring for children (Yunitawati & Latifah, 2017).

Changes in thyroid function can cause mood changes. Thyroid dysfunction can be seen from changes in thyroid levels and changes in thyroid stimulating hormone (TSH) in the blood. Most of these disorders occur as a result of impaired thyroid hormone synthesis. The thyroid gland produces thyroid hormone, which controls the speed of the body's metabolism. Hyperthyroidism indicates the excessive activity of the thyroid gland in synthesizing thyroid hormones, thereby increasing metabolism in the tissues. Subclinical hyperthyroidism is a condition in which a low serum thyrotropin (TSH) level (<0.5 mU/L) is found while free thyroxine (fT4) and free triiodotorin (fT3) levels are within normal limits. Hyperthyroidism is a condition in which there is a decrease and the secretion of thyroid hormone, resulting in a decrease in the body's metabolic rate (Rago et al., 2018) ; (Kotwal & Stan, 2018).

Thyroid hormones affect the function of neurotransmitters directly. Under normal circumstances, the thyroid hormone influences tissue metabolism, tissue oxidation processes, growth processes, and protein synthesis. This thyroid hormone affects all cells in the body through the mechanism of transport of amino acids and electrolytes from extracellular fluids into cells, activation/synthesis of protein enzymes in cells and increasing intracellular processes.

Changes in thyroid function will cause impaired cognitive function, behaviour, and changes in feelings (mood) and anxiety. Two-thirds of patients with thyroid disorders report that they have a psychiatric disorder. Several psychiatric disorders often appear in people with thyroid disorders: anxiety, depression, phobias, obsessive-compulsive disorder, and panic. The prevalence of anxiety disorders experienced by sufferers of thyrotoxicosis is around 33-61%, whereas, in hypothyroid sufferers, the problems encountered include depressive disorders or bipolar disorders (Struja et al., 2017). The hormone thyroxine produced by the thyroid gland maintains tissue metabolic rates for the normal functioning of cells and the body as a whole by stimulating O<sub>2</sub> consumption, protein synthesis and transcription of other genes in cells. The hormone thyroxine is said to be not essential for life. However, the absence of this hormone will cause setbacks and slow physical and mental growth (Liu et al., 2017).

Conversely, an excess of this hormone will cause the body to metabolize rapidly, causing tremors, nervousness, to excessive heat production. Hyperthyroidism is an endocrine disorder with the second-highest incidence rate after diabetes. Graves' disease is the most common cause of hyperthyroidism. Approximately 60% -80% of cases of hyperthyroidism are caused by Graves' disease, where women aged 20-50 are more dominant than men (Struja et al., 2017) ; (Srikandi, 2020).

Graves' disease is an autoimmune disorder; the presence of thyroid-stimulating immunoglobulin (TSI), or what is known as thyroid stimulating antibody (TSAAb), which is secreted in the thyroid gland, binds to thyroid stimulating hormone (TSH) receptors in the thyroid gland. Thus stimulating the thyroid gland to work, producing the hormone thyroxine based on stimulation from the TSH receptor. Continuous stimulation of TAb causes hyperthyroidism and thyromegaly. Almost all patients with Graves' disease have the classic symptoms of hyperthyroidism. Symptoms of orbitopathy or dermopathy are also present, but they do not stand alone without the classic symptoms of hyperthyroidism. Common symptoms that appear in patients at a young age include temperature intolerance, sweating, fatigue, weight loss, palpitations and tremors. In elderly patients, the symptoms will be vague and non-specific, such as fatigue or weight loss. Accompanied by extrathyroidal symptoms such as ophthalmopathy, dermopathy and osteopathy (Liu et al., 2017) ; (Pokhrel & Bhusal, 2017).

The test used to confirm Graves' disease is the calculation of the TSAAb. The elevation of TSI and thyrotropin-binding inhibiting (TBI) immunoglobulin has a sensitivity and specificity of 97% and 99% for diagnosing Graves' disease, respectively. In addition, an increase in iodine uptake on a Radioactive Iodine Uptake Scan with I-123 or I-131 can also be the basis for establishing a diagnosis (Dakkak & Doukky, 2017).

The initial laboratory test for diagnosis is a TSH-level test. If a low TSH is found, the recommended examination is FT4 and FT3 whenever possible. If testing is not possible, totals T4 and T3 can be used. Total T4 and T3 levels accompanied by a decrease in TSH will confirm the diagnosis of hyperthyroidism. History, physical examination and simple laboratory tests can enforce Graves' disease. ( 8,9) Presence of orbitopathy, diffuse enlargement of the thyroid gland with or without bruit and pretibial myxedema can be a strong enough basis for the diagnosis. However, a complete examination is still recommended if the signs and symptoms are not typical (Aung et al., 2019).

The primary therapy for Graves' disease is rapid reduction of hormone secretion and control of symptoms—three options for decreasing thyroid hormone production; Thionamides, Radioactive Iodine (RAI), and Thyroidectomy. Methimazole (MMI) and Propylthiouracil (PTU) are the most readily available drugs. This drug inhibits Thyroid Peroxidase (TPO) in the thyroid gland, inhibiting the synthesis of T4 and T3. PTU also inhibits conversion from T4 to T3 in peripheral tissues. At appropriate doses, 5-40 mg daily for MMI and 150-450 mg daily in three divided doses for PTU. Once thyroid function has improved, this drug can be tapped off to a euthyroid state. The maintenance dose of MMI is 5-10 mg per day, and PTU is 100-150 mg daily, divided into 2 to 3 times (Eliana et al., 2017).

RAI therapy is given to patients aged 21 years and over, not currently pregnant or even planning to become pregnant in the next year. Giving MMI is recommended first until the condition is close to the euthyroid, then stopping 3-5 days before giving RAI. With a fixed dose of I-131 10-25mCi, they have monitored every four weeks until the patient is hypothyroid. The levothyroxine maintenance dose will be given, and thyroid function will be re-examined in the next 6-12 months. Thyroidectomy is preferred for patients with large goitres (>80gr), anterior coli region suppression, cancer, or nodules larger than 4cm. Preparation for thyroidectomy is also the same as RAI; euthyroid conditions are sought,

and thyroid medication discontinuation is 7-10 days before removal. After the operation is complete, thioamides must be stopped and replaced with levothyroxine with an initial dose of 1.6 mcg/kg BW, then adjusted to TSH levels every six weeks of examination (Mallick et al., 2018)

Beta-adrenergic should be given to patients with typical symptoms of Graves' disease, especially those with an abnormal heart rate of more than 90x/minute, cardiovascular disease, and old age. Propranolol 10 mg 40 mg orally every 6 hours daily controls T3 and T4 in peripheral tissues.

Dysfunction of the Sinoarterial node (SA node, known as "Sick Sinus Syndrome ", is one of the causes of heart rhythm disturbances and can be caused by disturbances of either intrinsic or extrinsic factors of the SA node. The presence of heart rhythm disturbances establishes the diagnosis of Sick Sinus Syndrome. With episodes of tachycardia-bradycardia, accompanied by clinical symptoms such as syncope and palpitations, can be without clinical symptoms (De Regibus et al., 2016).

As we all know, the severe cardiovascular complications of hypothyroidism include coronary heart disease, ventricular arrhythmias, atrioventricular block, systolic myocardial weakness, pericardial effusion, low cardiac output and hypertension. Rarely, hypothyroidism can cause severe sick sinus syndrome that requires pacemaker treatment. Previous studies have also found that hypothyroidism can also cause mental disorders. We report a rare case of hypothyroidism accompanied by sick sinus syndrome (SSS) as a cardiovascular manifestation and severe mental disorder, both reversible and successfully treated with levothyroxine (Huang et al., 2021).

Therefore, the role of sick sinus syndrome (SSS) ECG in predicting the prognosis of Graves' disease is still being questioned. To address this issue, we undertook a systematic review to comprehensively evaluate the predictive role of sick sinus syndrome (SSS) ECG features in the prognosis of Graves disease.

## **METHODS**

This research is a Systematic Review using the Preferred Reporting Items for Systematic Reviews and Meta-analyses method, commonly called PRISMA; this method is carried out systematically by following the correct research steps or protocols. A systematic review is a method that uses reviews, studies, structured evaluations, classifications, and the categorization of evidence-based materials that have been produced previously. The steps in carrying out a systematic review are very planned and structured, so this method is very different from the method which conveys a literature study. The procedure for this systematic review consists of several steps, namely 1) compiling the Background and Purpose, 2) Research Questions, 3) Searching for the literature, 4) Selection Criteria, 5) Practical Screen, 6) Quality Checklist and Procedures, 6) Data Extraction Strategy, 7) Data Synthesis Strategy.

## **RESULTS AND DISCUSSION**

Based on previous research entitled Hypothyroidism and Complicated Sick Sinus Syndrome and Acute Severe Psychiatric Disorder: A Case Report aims to analyze rare cases of patients with severe hypothyroidism accompanied by sick sinus syndrome (SSS) as a cardiovascular manifestation that requires heart pacing and severe mental disorders. The population in this study was a 42-year-old woman who had hyperthyroidism and sick sinus syndrome with a mental disorder, using a rare case report analysis method. The study's results stated that the first reported case of hypothyroidism with sick sinus syndrome required a pacemaker and psychiatric disorders, and the symptoms could be improved and reversed after thyroxine supplementation. This case highlights the importance of

screening for hypothyroidism when dealing with unexplained psychosis or sick sinus syndrome, especially when combined.

The second study was conducted by (Tudoran & Tudoran, 2017), titled Hyperthyroidism and Sick Sinus Syndrome, a Rare but Challenging Association: A Study of Three Cases, which aimed to look at case reports aged 48 years, 63 years and 66 years. The population used in this study were female patients aged 48, 63, and 66 years who were brought to the emergency department by relatives using the case report analysis method in three cases. Based on the results showing that hyperthyroidism and SSS is a rare association, identified chiefly in patients with Graves' disease, even in the subclinical stage, it poses a therapeutic problem in the presence of concomitant tachyarrhythmias. Evolution is good in most cases after thyroid hormone normalization, rarely requiring pacemaker implantation.

The third study was conducted by (Kumar et al., 2021), entitled Sick sinus syndrome and Hyperthyroidism: A rare phenomenon. This study aims to look at case reports that are 70 years old. The population in this study was a 70-year-old female patient brought to the emergency department by her relatives. He has a history of feeling dizzy and lightheaded. He is a known case of diabetes mellitus, hyperthyroidism, hypertension, and atrial fibrillation with a controlled ventricular rate. With the research method using case reports, the study results show that hyperthyroidism and SSS are rare phenomena, especially among patients with Graves' disease. SSS/SA/AV node block can be corrected by treating hyperthyroidism to euthyroidism, which can obviate the need for a pacemaker. This case highlights the presence of SSS in hyperthyroidism followed by pacemaker implantation. With hyperthyroidism under control, the rhythm returns to normal and the pacemaker can eventually be removed.

The fourth study was conducted by (Tudoran & Tudoran, 2017) entitled An Adolescent Patient with Sick Sinus Syndrome Complicated by Hypothyroidism Carrying an SCN5A Variant A Case Report. This study aims to look at case reports that are 13 years old. The population in this study was a 13-year-old girl referred to our hospital due to bradycardia, as revealed by the school's screening electrocardiography (ECG). No ECG abnormalities had been observed during school screening conducted 3 years previously. She has had no episodes of syncope. For the past two years, she has noticed oedema on her face and lower legs and fatigue. An analysis of his growth curve also revealed that he experienced a slowdown in growth over these two years. There was no family history of arrhythmias, sudden death, or congenital heart disease. This study method is a case report, so the results show that In this report, we have presented a case of 13- a one-year-old girl with SSS who had variant SCN5A and also had developed hypothyroidism. The present case highlights the importance of genetic analysis, including for the SCN5A variant, in patients with hypothyroidism complicated by SSS or cardiac conduction disorders.

The fifth study was conducted by (Fukao et al., 2020) titled Graves' Disease and mental disorders. This research aims to see whether graves disease and mental disorders are related. The population in this study is a literature review of articles from 1985-2014. The study results the show that mental disorders, depression, and anxiety often coexist with GD. Psychosocial factors include stress and awareness of the illness, as well.

Biological factors, including the effects of thyroid hormone, may affect the course of the disease. Psychosomatic approaches, including antipsychotic medication and psychotherapy based on the medical bio-psycho-social model, are helpful in GD patients with mental symptoms concomitant with hyperthyroidism.

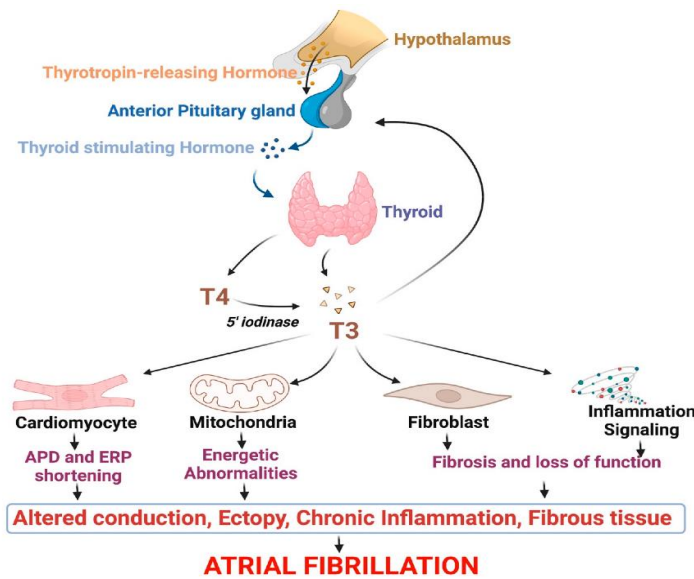
The sixth study was conducted by (Saramago et al., 2021) titled Digital Interventions for Generalized Anxiety Disorder (GAD): Systematic Review and Network Meta-Analysis. This study aimed to analyze Generalized anxiety disorder, the most common mental health condition, based on weekly prevalence. Digital interventions have been used as an alternative to or supplement conventional therapies to improve access, patient choice, and clinical outcomes. Little is known about their comparative effectiveness for generalizing anxiety disorders. The population in this study included 21 randomized controlled trials with 2,350 participants from the generalized anxiety disorder population. Due to the wide confidence intervals, the network meta-analysis results are inconclusive as to whether digital interventions are better than no intervention and non-therapeutic active controls, or whether they provide additional benefits to standard therapy. Future studies need to compare digital interventions with one-on-one therapy and non-digital manual self-help, including antidepressant medications as a treatment comparison and effects modifier.

The seventh study was conducted by (Rago et al., 2018) with the title Thyroid Ultrasonography: Consensus of the Italian Thyroid Association (AIT), Italian Society of Endocrinology (SIE), Italian Society of Ultrasonography in Medicine and Biology (SIUMB) and Ultrasound Chapter of Italian Society of Medical Radiology (SIRM). The analytical method used in this research is a Literature review. The results showed that the AS pattern of autoimmune thyroid disease was defined. Signs of US malignancy in thyroid nodules were classified and scored in each nodule. We also propose a simplified nodule risk stratification, based on the predictive value of each AS sign, classified and scored according to the strength of the association with malignancy, but also estimates of reproducibility between different carriers.

The eighth study conducted (Tudoran & Tudoran, 2017) was entitled Graves Disease with Heart Rhythm Disorders. Using the case report analysis method shows that Graves' disease is a metabolic disease that is not uncommon, especially in women aged 20-50 years. Diagnosis can be made by examining the history of the disease, physical examination and laboratory. Even with long treatment and continuous follow-up, the currently available drugs are proven to produce good outcomes for patients.

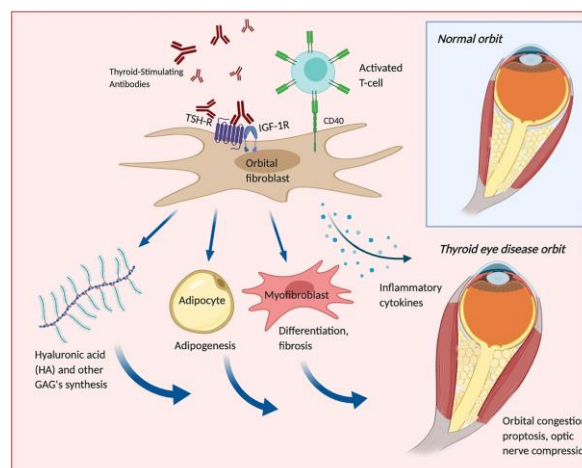
### **Characteristics of patients with Generalized Anxiety Disorder in Hyperthyroidism accompanied by Tonsillitis and Thyroid Eye Disease with ECG features of Sick Sinus Syndrome (SSS) in Children and Adults based on Age, Gender, and Pregnancy History.**

Research on hypothyroid, hyperthyroid, and groups of people with normal TSH shows that primary hyperthyroid sufferers have the most severe level of anxiety compared to other groups. Other studies state that patients with subclinical hyperthyroidism and subclinical hypothyroidism have higher anxiety scores than euthyroid subjects (Tudoran & Tudoran, 2017). This opinion differs from the results of other studies, which state that there is no relationship between thyroid disorders and mental disorders, depression and generalized anxiety disorder and the EKG picture of SSS accompanied by atrial fibrillation.

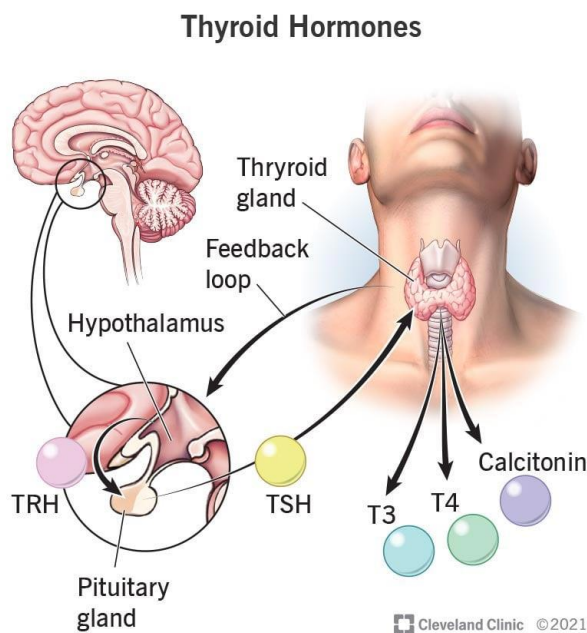


**Figure 1. Mechanism of Cardiovascular Disease on Hyperthyroidism**

The relationship between tonsillitis in hyperthyroid patients with disturbances of T3 and T4 hormones which in abnormal circumstances lead to tonsillitis infection accompanied by tonsillar hypertrophy of the tonsils after thyroidectomy in hyperthyroid patients. This is one of the complications that occur in treated hyperthyroid patients. With a history of panic disorder, an increase in electrochemical substances in the brain affects the production process of T3 and T4 hormones in hyperthyroid patients, which can cause symptoms, including thyroid eye disease. Patients who do not undergo surgery may experience tonsillar hypertrophy due to hyperplasia of the thyroid follicles, which diffuses to affect the tonsils' crypts, resulting in the tonsil glands' enlargement. The influence of a history of pregnancy from a mother who has a history of hyperthyroidism and treatment with thyroid therapy also affects the occurrence of hyperthyroidism in children later, with a significant risk of tonsillar hypertrophy due to the influence of mRNA chains that affect these children.



**Figure 2. Mechanism of Occurrence of Thyroid Eye Disease (Gohen, 2021)**



**Figure 3. Mechanism of thyroid hormone in the occurrence of tonsillitis (Cleveland, 2021)**

The relationship between generalized anxiety disorder and thyroid function has been discussed in several studies. Gonen et al. state that patients with subclinical hypothyroidism and subclinical hyperthyroidism have higher anxiety scores than euthyroid subjects. The results of Gonen's study are similar to this study. Namely, the anxiety scores of people with thyroid disorders are higher than those of euthyroid. Another study with almost the same results stated that the symptoms of anxiety and depression were felt more severely by people with overt hypothyroidism and overt hyperthyroidism. Research on hyperthyroid patients also showed that the hyperthyroid group had higher anxiety and depression scores than the euthyroid group.

## CONCLUSION

After a series of processes have been passed, based on research results in indexed journals Scopus and Sinta regarding a systematic review of the Characteristics of Patients with Generalized Anxiety Disorder in Hyperthyroidism with Tonsillitis accompanied by Thyroid Eye Disease with EKG Sick Sinus Syndrome (SSS), it can be concluded that the majority of journals discuss age, Gender is associated with risk factors for hyperthyroidism. From the sub-chapters, it can be concluded that the risk factors for hyperthyroidism are determined based on age, sex, and lifestyle. Moreover, hyperthyroidism is associated with generalized anxiety disorder and the EKG picture of Sick Sinus Syndrome.

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