Case report

"A PITUITARY STALK INTERRUPTION SYNDROME LEADING TO METABOLIC DYSFUNCTION ASSOCIATED STEATO- HEPATITIS"

Commented [DO1]: Pituitary Stalk Interruption Syndrome Presenting with Metabolic Dysfunction-Associated Steatohepatitis: A Case Report

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ABSTRACT

Background:
Pituitary Stalk Interruption Syndrome (PSIS) is a rare congenital disorder characterized by the absence or thinning of the pituitary stalk, hypoplasia of the anterior pituitary, and ectopic posterior pituitary. This results in panhypopituitarism and related clinical manifestations. Emerging evidence suggests an association between PSIS and metabolic dysfunction, potentially progressing to advanced liver disease.
Case Report:
We present the case of a 31-year-old female with a known diagnosis of panhypopituitarism due to PSIS (diagnosed in 2014), with a history of primary amenorrhea and multiple episodes of adrenal insufficiency. She presented with complaints of fever, vomiting, and yellowish discoloration of the eyes. Clinical examination revealed icterus, right hypochondriac tenderness, hepatomegaly, and Cushingoid features. Laboratory evaluation demonstrated dyslipidaemia, hyperglycaemia, hyperbilirubinemia, and elevated liver enzymes. Imaging revealed hepatomegaly with severe hepatic steatosis. After exclusion of other common aetiologies of hepatitis, a liver biopsy was performed, confirming severe steatosis with fibrosis. A final diagnosis of metabolic dysfunction-associated steatohepatitis (MASH) secondary to PSIS was made.
Conclusion:
The pathophysiological link between PSIS and metabolic dysfunction-associated steatotic liver disease (MASLD) has been reported shortly. Proposed mechanisms include altered STAT signaling pathways (e.g., STAT1/3 activation, STAT5 inhibition) leading to impaired hepatic lipid metabolism and increased insulin resistance. Evidence suggests that MASLD may progress more rapidly in patients with PSIS compared to other aetiologies. Hormone replacement therapy (HRT) remains the cornerstone of management and may help slow disease progression. Early recognition, routine liver function monitoring, and timely intervention are essential to prevent long-term hepatic complications in patients with PSIS.

Commented [DO2]: The term MASH inherently indicates association with metabolic dysfunction, so secondary to PSIS" needs to be clarified as a possible contributory factor, not a primary cause

Commented [DO3]: MASLD is used in the conclusion, while MASH is used earlier.These are distinct terms. MASLD (Metabolic dysfunction-associated steatotic liver disease) is the broader category, and MASH is a progressive subtype involving inflammation and fibrosis. Be consistent and accurate.

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Keywords:- *Panhypopituitarism, PSIS, Metabolic dysfunction associated steatotic liver disease, Hormone Replac therapy*

1. INTRODUCTION

PITUITARY STALK INTERRUPTION SYNDROME (PSIS) is a rare congenital disorder causing panhypopituitarism due to **anterior pituitary hypoplasia, interrupted pituitary stalk and an ectopic posterior pituitary**. It leads to multiple endocrine deficiencies and metabolic disturbances, including insulin resistance and dyslipidaemia[(1)].

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We report a female in her early 30s with PSIS diagnosed in 2014, presenting with icterus, fever, and vomiting. She had a history of primary amenorrhea and multiple adrenal insufficiency episodes. Examination revealed hepatomegaly, cushingoid features and right hypochondriac tenderness. Laboratory tests showed dyslipidaemia, hyperglycaemia, and elevated liver enzymes. Imaging and biopsy confirmed severe steatosis and fibrosis, leading to a diagnosis of **Metabolic Dysfunction-Associated Steato-hepatitis (MASH)** secondary to PSIS.

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The exact mechanism linking PSIS to MASH remains unclear, but altered hepatic fat metabolism and insulin resistance through STAT pathway dysregulation has been proposed. Early recognition and **hormone replacement therapy (HRT)** are crucial in preventing progression. This case highlights the need for routine liver function monitoring in PSIS patients to detect metabolic liver disease early.

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2. CASE PRESENTATION

PRESENTING HISTORY:-

A woman in her early 30s presented to our outpatient department with a two-week history of progressive yellowish discoloration of the eyes, intermittent fever (up to 38.5°C), right upper quadrant abdominal pain, and vomiting (3–4 episodes daily, non-bilious). She denied recent weight loss, altered bowel habits, or alcohol use. Her symptoms began insidiously, with fatigue preceding the onset of jaundice by one week.

She was diagnosed with PSIS in 2014 during evaluation for primary amenorrhea. Initially compliant with HRT (including steroids and estrogen), she discontinued therapy after achieving menarche, leading to secondary amenorrhea and recurrent adrenal insufficiency episodes (3–4 over the years). During these episodes, she received short-term steroids (e.g., hydrocortisone for one week) but did not maintain long-term therapy. She had no history of diabetes mellitus or alcohol consumption, was married for 5 years but nulligravid, and followed a mixed diet. Her developmental history was unremarkable, with attainment of mid-parental height and near-normal secondary sexual characteristics.

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EXAMINATION FINDINGS

On examination, she was obese (BMI 29 kg/m²), conscious, and oriented, with stable vital signs (blood pressure 110/70 mmHg, pulse 70/min, respiratory rate 14/min, SpO_2 99%, capillary blood glucose 220 mg/dL). She had icterus and Cushingoid features (moon facies, buffalo hump, central obesity, purple abdominal striae) **(Fig 1)**.

Abdominal examination revealed tender hepatomegaly (4 cm below the right costal margin). Breast examination showed Tanner stage III development, while genital examination indicated Tanner stage I pubic hair with normal external genitalia. Fundoscopy, performed due to new-onset hyperglycaemia, showed no diabetic retinopathy.

DIAGNOSTIC CONSIDERATIONS

Given her history of pituitary dysfunction, features of metabolic syndrome, and new-onset liver involvement, we considered **Acute hepatitis for evaluation, metabolic syndrome** in our differential diagnosis. *The presence of cushingoid features without chronic steroid intake raised concerns regarding endogenous hormonal imbalances contributing to her metabolic derangements*. Hence, she was evaluated further to determine the aetiology of her acute hepatitis.

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INVESTIGATIONS **(TABLE-1)**

(TABLE-1- Investigation panel)

LAB INVESTIGATIONS	RESULTS	REFERENCE RANGE

Liver function tests:		
Total bilirubin	**4.6 mg/dl**	0.3 - 1 mg/dl
Direct bilirubin	**2.4 mg/dl**	0.1 - 0.3 mg/dl
AST/ALT	**186/65 IU/L**	10-40 / 10-40 IU/L
ALP	**133 IU/L**	30-120 IU/L
Total Protein/Albumin	7.7/4.3 g/dL	5.5-9 / 3.5-5.5 g/dL
PT/INR/APTT	13.54 s /0.9/28.5 s	11-13 s/0.8-1.1/25-35 s
Haemoglobin	11.9 g/dl	12 – 16 g/dl
Platelet	**96000/µL**	150000 -450000 /µL
WBC	13600/µL	4000-11000 /µL
VIRAL MARKERS PANEL (HbsAg, Anti-HCV,HIV, IgM anti HAV,HEV, IgM-CMV,EBV,HSV)	**NEGATIVE**	
TROPICAL ILLNESS PANEL (SCRUB typhus, LEPTO MAT, QBC smear)	**NEGATIVE**	
Auto immune Hepatitis Panel (ANA, SMA, ANTI- LKM 1)	**NEGATIVE**	
24 hr Urinary Copper	15 µg in 24 hrs	0-100µg / 24hrs
S. Alpha 1 anti trypsin	150 mg/dL	150-350 mg/dL
S. Ferritin	100 ng/mL	24- 307 ng/mL
S. IgG	900 mg/dL **(WNL)**	800-1500 mg/dL
Glycaemic profile:-		
Fasting blood sugar	**250mg/dL**	70-99 mg/dL
Post prandial blood sugar	**300 mg/dL**	<140 mg/dL
HbA1C	**7.5 %**	4-5.6 %
Fasting Lipid Profile:-		
Triglycerides	**456 mg/dL**	**<100 mg/dL**
Total Cholesterol	**278 mg/dL**	**<200mg/dL**
High density Lipoprotein	**27 mg/dL**	**>60 mg/dL**
Urine Albumin- Creatinine ratio (ACR)	20 mg/g	< 30mg/g
HORMONAL PANEL (BELOW NORMAL LIMITS)		

Thyroid function test S. TSH S. FT4	 5.00 µIU/mL 0.6 ng/dL	 0.5-4 µIU/mL 0.8- 1.8 ng/dL
S. Cortisol (8am)	**1.86 µg/dl**	5 – 25 µg/dL
S. LH S. FSH S. ACTH (after ACTH stimulation test)	<0.07 IU/L 0.32 IU/L 3 pg/mL	1.9- 12.5 IU/L 1.1-9.9 IU/L 9-52 pg/mL
S. Oestradiol S. Progesterone	15 pg/ml <0.21 ng/mL	40-200 pg/mL 2-30 ng/mL
S. Testosterone	<2 ng/dL	18-54 ng/dL
S. GH (after Insulin tolerance test) S. IGF-1	0.06 ng/mL 25 ng/mL	>7 ng/mL 114- 492 ng/mL
ECG:-	Heart Rate -90bpm, normal axis, normal sinus rhythm, no ST-T segment changes	

Abbreviations:-

ng- nanogram, pg- picogram, mg- milli gram, dL- decilitre, mL- millilitre, IU- International Unit, µ-micro, AST- Aspartate aminotransferase, ALT- Alanine aminotransferase, ALP- Alkaline phosphatase, PT- Prothrombin time, INR- International normalised ratio, APTT- Activated partial thromboplastin time, WBC- White blood cells, HbsAg- Hepatitis B virus surface antigen, Anti-HCV- Anti hepatitis C virus antibody, HIV- Human immunodeficiency virus, anti HAV-Hepatitis A virus ,HEV- Hepatitis E virus, CMV- Cytomegalovirus, EBV- Epstein barr virus, HSV- Herpes simplex virus, LEPTO MAT- Leptospirosis Microscopic agglutination test, QBC- Quantitative buffy coat smear for malaria, ANA- Anti nuclear antibody, Anti-SmA – Anti Smooth muscle antibody, Anti- LKM 1—Anti Liver kidney microsomal -1 antibody, IgM- Immunoglobulin M, IgG- Immunoglobulin G, HbA1C- Glycated haemoglobin, GH- Growth Hormone, LH- Luteinizing hormone, FSH- Follicle Stimulating Hormone, ACTH- Adrenocorticotropic hormone, TSH- Thyroid Stimulating hormone, FT4- Free thyroxine T4, IGF- Insulin like Growth factor -1, ECG- Electrocardiogram WNL- Within normal limits

Fig. 1: Cushingoid body habitus *(purple abdominal striae)*

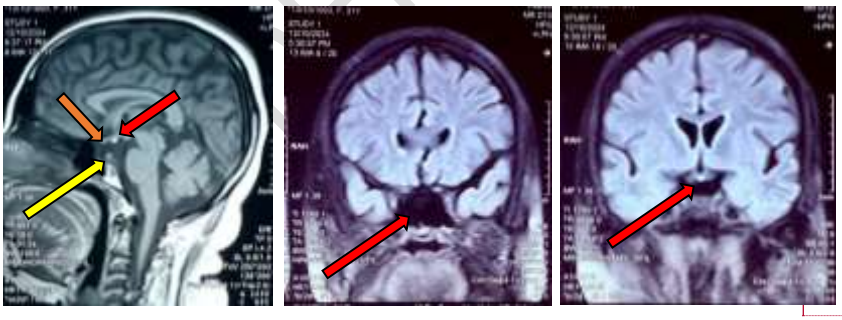

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Fig. 2: Findings on pituitary magnetic resonance imaging(MRI) *2.1 sagittal T1W shows hypoplastic small anterior pituitary (yellow arrow),interrupted pituitary stalk(orange arrow), ectopic posterior pituitary (red arrow) ; 2.2 flair coronal T1WI hypoplastic anterior pituitary(red arrow); 2.3 flair coronal T1WI hypoplastic ectopic posterior pituitary(red arrow);*

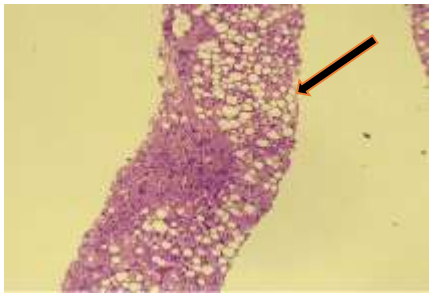

Fig. 3: Liver Biopsy. H&E stain: Deranged liver architecture with Hepatocytes showing *severe macro vesicular hepatitis (black arrow)*

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IMAGING MODALITIES:-

- **USG ABDOMEN –** Hepatomegaly with Grade III fatty liver, No free fluid **;** Bilateral kidneys –normal size and echoes
- **PORTAL VENOUS DOPPLER –** Normal study
- **CT ABDOMEN: Hepatomegaly** with severe steatosis

  Liver attenuation index – (-10) - (suggestive of moderate to severe steatosis)
- **FIBROSCAN – Fibrosis grade F3 (10 kPa), CAP score- steatosis grade – S2 (266 dB/m)**
- **MRI PELVIS-** Hypoplastic uterus & ovaries
- **MRI BRAIN**[(Fig.2)-] *Features suggestive of PSIS* (absent pituitary stalk, hypoplasia of the anterior pituitary and an ectopic posterior pituitary)

As all other causes of Acute hepatitis were ruled out, also patient fulfils the criteria for metabolic syndrome (increased waist circumference and triglycerides, low HDL) and imaging modalities revealed- severe hepatic steatosis, we proceeded for liver biopsy

LIVER BIOPSY(Fig.3):-

Deranged liver architecture with hepatocytes showing severe macro vesicular steatosis (> 66%, score 3). On Masson trichrome, portal fibrosis with bridging septae & incomplete nodule formation +. Perl's reaction (Iron)/ Rhodanine stain (copper) - negative .

Final report- Steatotic liver disease, Possibility of Non-alcoholic steato-hepatitis. NAS score: 6/8. Fibrosis score: F3(out of 4)

5DIFFERENTIAL DIAGNOSIS

Getting into the causes of hepatitis, *all common causes* like viral infections, tropical illnesses, auto-immune hepatitis, Metabolic liver disease like Wilsons, hemochromatosis, alpha 1 antitrypsin deficiency were ruled out with the above investigation panel. Patient was diagnosed with *new onset diabetes mellitus, dyslipidaemia (Metabolic syndrome) and anterior pituitary hormonal deficiency* **(significantly cortisol levels were on the lower side).** After this extensive workup, as patient did not have a history of diabetes or metabolic syndrome prior, following a thorough review of the literature to determine the underlying cause of severe hepatic steatosis and fibrosis in a young patient without traditional risk factors, we **identified a direct relationship between pituitary stalk interruption syndrome and metabolic dysfunction-associated steato-hepatitis.** Various novel mechanisms, including alterations in hepatic fat metabolism and insulin resistance, have been proposed to explain this association.***The patient was ultimately diagnosed with Pituitary stalk interruption syndrome leading to metabolic dysfunction-associated steato-hepatitis (MASH)/Newly diagnosed Diabetes Mellitus***

TREATMENT

The patient was initiated on thyroxine, corticosteroids, growth hormone, oral anti diabetic agents, and lipid-lowering therapy. Oestrogen and progesterone supplementation were deferred until resolution of the acute hepatitis.

OUTCOME AND FOLLOW-UP

With treatment, jaundice resolved completely by the second month and hormone therapy was fully optimized. The patient showed significant clinical improvement and has been kept under follow-up periodically screening her liver and hormonal parameters in an out-patient basis.

This case highlights a rare but critical cause of progressive liver disease, where timely hormone replacement therapy offers a unique opportunity to prevent cirrhosis and its complications at a young age. Routine monitoring of liver function and endocrine status is essential in patients with pituitary stalk interruption syndrome to facilitate early intervention

3. DISCUSSION

Pituitary Stalk Interruption Syndrome (PSIS) is a rare congenital anomaly with an incidence of 0.5 in 1,00,000 live births [(1)] characterized by **triad in MRI Brain such as thinning or disappearance of the pituitary stalk, anterior pituitary hypoplasia and an ectopic posterior pituitary**. The most common ectopic position is the median carina[(2).] *Perinatal adverse events* such as breech delivery, hypoxia, dystocia (traumatic birth events) etc., may play a role in the occurrence and development of PSIS.

Genetic implications for PSIS have been found out. PSIS related gene mutations have been reported, including in *HESX1*, *OTX2*,*SOX3*, *LHX4*,*PROP1*, *PROKR2*, *CDON*, holoprosencephaly related gene *TGIF, SHH*, *GPR161*and *ROBO1*. It can also be due to a polygenic cause. Chromosome abnormalities like 18p deletion, 2p25 duplication, 2q37 deletion and 17q21.31 microdeletion have also been implicated.[(1)]

CLINICAL FEATURES:-

PSIS in *neonates* can be manifested in form of Neonatal jaundice, hypoglycaemia and cryptorchidism or micropenis. Patients may present with *isolated or combined anterior pituitary hormone deficiencies* such as GH(most common), LH,FSH, ACTH, TSH presenting as dwarfism, absence of secondary sexual characteristics, adrenal insufficiency episodes, hypothyroidism etc.,[(3)] The posterior pituitary gland generally has normal function and diabetes insipidus is rare. Some patients will get complicated *with midline structural abnormalities* and other cranio-facial malformation, such as corpus callosum atrophy, dysplasia of septum pellucidum, cleft lip, etc.,[(2)] .On the other hand, patient can develop metabolic syndrome which would , further lead *to MASH*

PSIS and MASH – Mechanisms:-(1,4)

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become a prominent global health challenge. It is characterised by excess accumulation of hepatic lipids (hepatic steatosis), which can lead to inflammation (steato-hepatitis) and progressive fibrosis. Overlap between metabolic dysfunction-associated steato-hepatitis (MASH) and these endocrinopathies lead into the proposal of multiple novel mechanism which are explained as follows:-

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Growth Hormone(GH) and MASLD

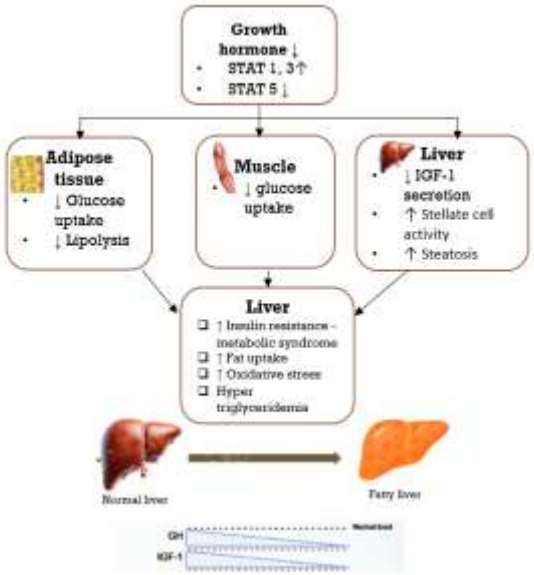

Fig 4 – Growth Hormone and MASLD Mechanisms (self drawn using MS Powerpoint)

GH is produced in a pulsatile fashion by the anterior pituitary which in turn stimulates the production of *IGF-1 via JAK2, STAT-5* primarily in hepatocytes[4]. **IGF-1** is responsible for reducing visceral fat, decreasing lipogenesis, improving insulin sensitivity, improves senescence of hepatic stellate cells- thereby reducing steatosis and fibrosis (Fig- 4). Individuals with GH deficiency can progress into metabolic syndrome, insulin resistance, hepatic steatosis and progressively fibrosis. Ceramides inhibits Akt 2 phosphorylation and downstream insulin signalling, diacylglycerol activates protein kinase C – both being the key pathway for developing insulin resistance by increasing the oxidative stress[5]

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Thyroid hormone and MASLD

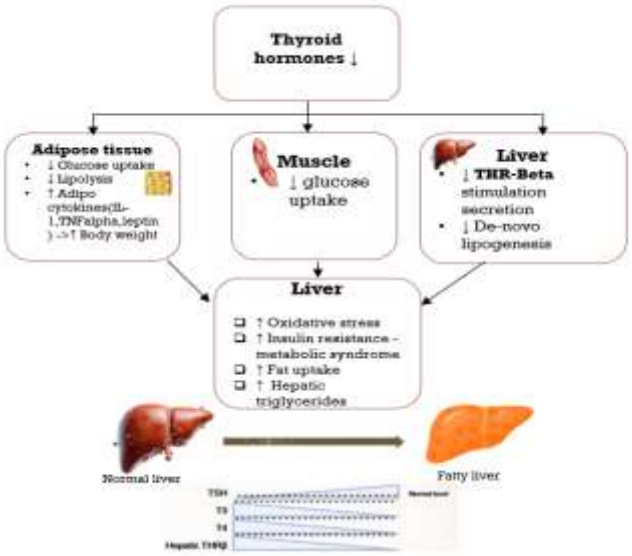

Fig 5- Thyroid hormone and MASLD mechanisms (self drawn using MS Powerpoint)

It has been reported that the prevalence of central hypothyroidism in patients with PSIS is 79.8 %, but another study found that only 5.6 % of PSIS patients with hypothyroidism have low TSH levels[1]

Thyroid hormones are involved in various metabolic process including body fat distribution, lipid utilization and glucose homeostasis. Also, the *THR- beta receptor present in liver is responsible for its action in the liver.* Lower thyroxine levels, leads to decreased THR – beta stimulation(4), in turn leading to increased oxidative stress, fat uptake, metabolic syndrome leading to MASH which may further progress to MASLD and cirrhosis (Fig -5) . THR – Beta agonist – **Resemitrom** -recently FDA approved drug for MASH in 2024

Gonadal hormones and MASLD :-

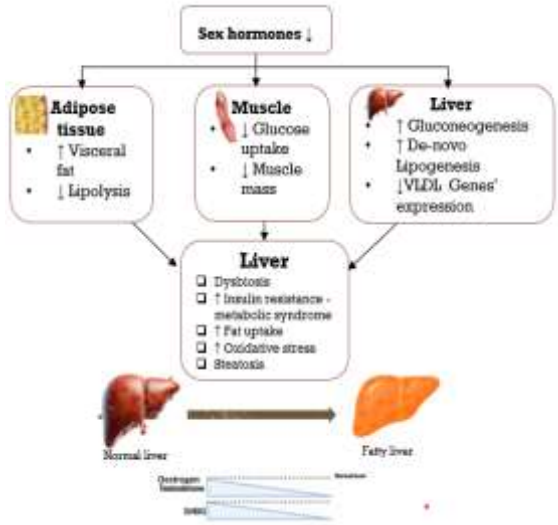

Fig 6 - Sex hormones and MASLD mechanisms (self drawn using MS Powerpoint)

Oestrogen plays an important role in hepatic lipid metabolism. Studies found that the prevalence of metabolic syndrome and MASLD in post- menopausal women has been increased. Hence, Oestrogen deficiency leads to decreased hepatic and muscle insulin sensitivity resulting in the progression of steatosis and further to CLD.

Androgen deficiency increases de-novo fat synthesis in liver and decreased expression of VLDL genes, thereby leading to steatosis. Also, it has an impact on intestinal microbiota such as increase in the ratio of firmicutes to bacteroides and an increase of lactobacillus species in the cecum. These microbes in the intestine maintains the Glucagon – like peptide-1 *(GLP-1) levels* thereby regulating insulin resistance[1]. Decrease in these, can lead to metabolic syndrome further to MASLD (Fig-6)

OTHER HORMONES AND MASLD:- [6–18]

Prolactin has a positive effect on hepatic metabolism through PRL receptor mediated *inhibition of fatty acid translocase/CD36*. Its deficiency is associated with increase in CD 36 associated with development of insulin resistance progressing to steatosis [1]

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Steroids use in the treatment of PSIS related MASLD is found to be a double-edged sword that increased or high dosage steroids itself has a probability of transforming to cirrhosis. So, the dosage must be titrated adequately & their liver chemistries must be monitored closely on a frequent basis.

MANAGEMENT:-
REPLACEMENT THERAPY:- [20]
The following are the recommended treatment modalities for this condition:

1. *ACTH deficiency*:- Hydrocortisone – 10-20mg daily in divided doses, Cortisone acetate- 15-25 mg/day in divided doses
2. *TSH deficiency*:- L-Thyroxine 0.05-2mg daily (according to T4 levels)
3. *FSH/LH deficiency*:- Males—Testosterone enanthate 200mg IM every 2-3 weeks, Testosterone undecanoate 1000mg IM every 3-6 months, Testosterone skin patch 2.5-5 mg/day; Females- Oestradiol skin patch 4-8mg twice weekly, Oestradiol gel, Conjugated oestrogen 0.65mg daily, Micronized oestradiol 1mg daily, Oestradiol valerate 1-2mg
4. *For fertility* – Males :- hCG three times weekly, or hCG + FSH or Menopausal gonadotropin or GnRH / Females :- Menopausal gonadotropin ,hCG or GnRH
5. *GH deficiency* :- Adults- Somatotropin 0.2-1mg S.C daily, Children- Somatotropin 0.02-0.05 mg/kg/day
6. THR – BETA AGONIST – **RESEMITROM** -recently FDA approved drug for MASH in 2024

Clinical trials of MASH -FGF 19 ANALOG – ALDAFERMIN,PPAR AGONIST- LANIFIBRANOR, ELAFIBRANOR,GLP-1 AGONIST- LIRAGLUTIDE, SEMAGLUTIDE, CCR 2/5 INHIBITOR – CENICRIVIROC, FXR AGONIST – TROPIFEXOR, CILOFEXOR (The above drugs are under phase 2 clinical trials for MASH)

CONCLUSION:-

- **Panhypopituitarism can present with or exacerbate MASH**, and should be considered in patients with unexplained hepatic steatosis, especially when accompanied by features of pituitary hormone deficiencies.
- **Common causes of hepatitis, including viral, autoimmune, and metabolic aetiologies, must be thoroughly excluded** before attributing liver dysfunction to endocrine causes like panhypopituitarism.
- **Timely initiation of tailored hormone replacement therapy is essential**, as it not only addresses systemic symptoms but may also halt or reverse hepatic injury progression in MASH associated with endocrine dysfunction.
- **Liver function monitoring should be part of routine follow-up in patients with panhypopituitarism**, particularly in those with risk factors for metabolic dysfunction or evidence of hepatic involvement.

CONSENT (WHERE EVER APPLICABLE)

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable

ABBREVIATIONS:-

PSIS- Pituitary Stalk Interruption Syndrome
MASLD- Metabolic dysfunction-associated steatotic liver disease
STAT- Signal Transducer and Activator of Transcription
HRT- Hormone Replacement Therapy
GH- Growth Hormone
LH- Luteinizing hormone
FSH- Follicle Stimulating Hormone
ACTH- Adrenocorticotropic hormone
TSH- Thyroid Stimulating hormone
THR- Thyroid hormone receptor
IGF- Insulin like Growth factor -1
THR- Thyroid hormone receptor
JAK- Janus Kinase
CLD- Chronic Liver Disease
GLP- Glucagon – like peptide-1
VLDL- Very low-density lipoprotein
FGF-19- Fibroblast growth factor
CCR- Chemokine receptor
FXR – Farnesoid X Receptor
GnRH- Gonadotropin Releasing Hormone
hCG- Human Chorionic Gonadotropin
F/S/O- Features suggestive of
WNL- Within Normal Limits
H & E- Haematoxylin and Eosin Stain
NAS score - Non-alcoholic fatty liver disease score
CAP- Controlled attenuation parameter

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