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ESE young endocrinologists and scientists
looking forward

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EYES 2024 Annual Meeting, Helsinki, Finland, 6-8 September 2024

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CONTENTS

17 The characteristics of 541 severe hypoglycaemia's presentation and management underscore the need for improved services: Pilot data from DEKODE Hypoglycaemia study
96 Association Between Glycemic Control Parameters and Diabetic Macular Edema in Type 1 Diabetes: A Retrospective Study using CGM data
64 Long COVID is associated with accelerated aging in type 2 diabetes patients
48 There is a need for better Implementation of DKA Guidelines - Findings from the DEKODE DKA Study
137 Partial familial lipodistrophy - 2 case reports
66 Low mitochondrial DNA is associated with post-COVID-19 syndrome in patients with type 2 diabetes
94 Normocytic Anemia and Its Associated Factors Among Type 2 Diabetes Mellitus
13 Diabetic striatopathy in a patient with uncontrolled hyperglycemia: A rare case report
62 An animal model for Heart Failure with preserved Ejection Fraction (HFpEF)

Interdisciplinary Endocrinology

29 Similar Recurrence and Survival in Pre- and Post-Renal Transplant Papillary Thyroid Cancer: Data From a 1507 Recipient Registry
129 Retinal Microvascular Changes with OCT Angiography and Serum Gremlin-1 Levels in Acromegaly: a Case-Control Study
51 Putting two and two together: a rare case of McCune-Albright syndrome
49 Revealing Fahr's Syndrome in a Patient Previously Misdiagnosed and Treated for Epilepsy: a Case Report
136 In vitro evaluation of the HEK293 cell line as a model to measure glucocorticoids activity
132 Complexity and multimorbidity in autoimmune polyendocrine syndrome type 2 - a case report

Pituitary and Neuroendocrinology

110 Growth With Something Other Than Growth Hormone in Children With Craniopharyngioma
35 Cannulated prolactin a forgotten test which can be cost saving
108 Double Trouble: Adipsic Diabetes Insipidus and Panhypopituitarism in Isolated Hypothalamo-Pituitary Langerhans Cell Histiocytosis
117 Neurocognitive and Neuropsychological Assessment in the Acromegalic Patient: Correlation with the Clinical, Biochemical and Prognostic Features
25 Efnb2 controls pituitary development by regulating the pituitary stem cell niche
135 Unforeseen Depths of Short Stature: A Case study
104 Pituitary Microadenoma in Children - Diagnostic Challenges and Traps

Reproductive Endocrinology

88 Induction of spermatogenesis in men with hypogonadotropic hypogonadism
23 Previous illicit androgen users display persistently impaired Leydig cell capacity but recovered luteinising hormone secretion
50 Variations in the assessment and education of polycystic ovary syndrome (PCOS) during initial consultations across Europe and India: A multinational study
28 Testosterone serum levels predict the severity of metabolic dysfunction-associated steatotic liver disease (MASLD) in hypogonadal men
75 Tamoxifen Use in Gynecomastia: A Tertiary Centre Experience
71 Copy Number Variations in Self-Limited Delayed Puberty
100 Short-term changes in bone metabolism among transgender men starting gender affirming hormone therapy: a systematic review and meta-analysis
40 Tyrosine kinase inhibitors: systematic review of their effects on male gonadal function
54 Is menopause the answer for a 47 year old woman?
68 Anogenital Distance in Klinefelter Syndrome: A Case-Control Study

Thyroid

123 Evaluating Predictive Models for Radioiodine Therapy Success in Differentiated Thyroid Cancer Patients
58 Alterations in Gut Microbiome in Patients with Autoimmune Thyroiditis with Hypothyroidism and Irritable Bowel Syndrome with Constipation
18 Unveiling The Mystery of a Thyroid Nodule: A Case Report
146 Challenging reference values for basal and stimulated calcitonin in medullary thyroid cancer diagnosis: a 2 center experience from real life setting

36 Metastasis of Clear Cell Renal Cell Carcinoma to the Thyroid Gland Resembling Papillary Thyroid Cancer: A Case Report
144 Ultrasound Guided Percutaneous ethanol injection (PEI) for the Treatment of Cystic and Predominantly Cystic Thyroid Nodules: A single centre experience
41 Non-Thyroidal Illness Syndrome in SARS-CoV-2 infection: Insights from a COVID-19 dedicated hospital at the peak of the pandemic
103 Thyroid Hormones Regulate the Transcriptome of Infiltrating Microglia
126 The largest case of exophytic lymph node papillary thyroid cancer metastasis: a multidisciplinary approach from diagnosis to treatment
106 Lipid profile in subclinical and overt hypothyroidism
139 A Case Report: Thyroid Storm with Severe Heart Failure and Atrial Fibrillation Treated by Thyroidectomy After Plasma Exchange
161 Therapeutic plasma exchange as a bridge to radioactive iodine treatment in a patient with severe thyrotoxicosis and serious adverse effects to antithyroid drugs: a case report

Adrenals and Neuroendocrine Tumors

16

Unilateral gynecomastia unveiling an adrenal finding: a case report of a large adrenal oncocytic tumour

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Introduction
We report a case of a 72-year-old man who was incidentally discovered to harbour a large right adrenal mass during evaluation for resistant hypertension and subsequently diagnosed with an androstenedione and oestrogen secreting adrenocortical tumour.
Case report
A 72-year-old gentleman presented with unilateral gynecomastia which was previously investigated with a mammogram and biopsy (normal) to rule out breast cancer. Two years later, he presented to the cardiology department with poorly controlled hypertension and shortness of breath. He had history of ischemic heart disease, heart failure with preserved ejection fraction. His cardiac MRI revealed an incidental right-sided adrenal mass measuring 12 × 15 × 18 cm. He was referred for endocrine evaluation which identified significantly elevated dehydroepiandrosterone sulphate >27 µmol/l [0.91 -6.76], androstenedione 33.2 nmol/l [1.5-6.5], oestradiol 421 pmol/l [95-233], and progesterone 1.2 nmol/l [0.2-0.5]. FSH was suppressed 1.3 IU/l [1.5-12.4] with normal LH 1.9 IU/l [1.7-8.6]. Plasma renin activity 1.9 nmol/l/hr [0.5-3.5 nmol/l/hr], aldosterone 250 pmol/l [90-700 pmol/l], plasma metanephrines, metadrenaline 122 pmol/l [80-510], normetadrenaline 555 poml/l [120-1180 pmol/l], 3-methoxytyramine <180 pol/l [<180 pom/l] and 9 am cortisol 299 nmol/l [172-497 nmol/l] levels were all within normal range. A FDG PET-CT scan showed avid uptake by the adrenal mass, suggestive of a metabolically active lesion, an I-123 MIBG scan showing the mass was non-avid. A multidisciplinary discussion by the adrenal team meeting (MDT) resulted in a decision to proceed with a right adrenalectomy which happened uneventfully. Postoperative hormone profile showed a marked reduction in dehydroepiandrosterone sulphate and oestradiol levels to 0.7 µmol/l and 206 pmol/l respectively. Histological examination confirmed an oncocytic adrenocortical tumour with Ki-67 index 3%. The surveillance imaging showed a residual lesion accompanied by a normal repeat hormonal profile. He is scheduled for a repeat FDG PET scan in June 2024 to monitor for potential tumour recurrence.
Conclusion
Adrenal oncocytic neoplasms (AON) are indeed rare tumours, with only around 287 cases reported in the literature. Among these cases, only 30% display metabolic function, with hyperandrogenism and Cushing syndrome observed in 13.2% and 8% of AON patients, respectively. This case underscores a delayed diagnosis and an incidental finding during cardiovascular assessment, highlighting the significance of a thorough diagnostic evaluation that includes imaging and hormonal profiling for conditions like gynecomastia and resistant hypertension. By contributing to the global literature, this case report emphasizes the crucial role of adrenal surgery in managing these rare solid neoplasms.

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97

Pheochromocytoma diagnosed during pregnancy – a case report

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Introduction
In pregnancy, pheochromocytoma is an extremely rare clinical condition. If undiagnosed and nontreated, it's associated with adverse maternal-fetal outcomes. An early diagnosis and the prevention of a hypertensive crisis during delivery and surgical treatment are of the utmost importance in the management of a pheochromocytoma during pregnancy.
Case report
We report the case of a 41-year-old female diagnosed with pheochromocytoma during pregnancy at week 36 of gestation. She presented with episodes of headache, palpitations, sweating and paroxysmal hypertension. She previously had hypertensive crisis after surgical procedures (myomectomy, c-section). Blood tests showed elevated plasmatic and urinary metanephrines (6-fold above normal cut-offs). MRI revealed a left adrenal mass with 3,7 × 2.5 × 2 cm suggestive of a pheocromocytoma. A C-section was performed after 7 days of α-blockade with phenoxybenzamine (37 weeks of gestation) and she underwent laparoscopic left adrenalectomy 2 weeks post-partum. The pathology study confirmed the diagnosis. Post-surgical study showed normal metanephrines. Genetic study is underway.
Discussion and conclusion
The management of pheochromocytoma during pregnancy is challenging: optimum timing of surgery, preferred route and timing of delivery and type of α-adrenergic receptor blockers during pregnancy are not consensual. Decisions should be made on an individual basis. Our case demonstrates that a multidisciplinary approach to adopt the right pre and post-operative treatment, improves both maternal and fetal outcomes.

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87

How ready are endocrine scientists to share clinical data for research: a europe-wide study throughout the adrenal tumor research consortium

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Context
Medical data sharing is central for clinical research. Physicians have always shared data for multicentric retrospective studies. However, in the current framework, clinical data exchange requires a complex set-up, featuring interoperability, security, ethical and legal compliance.
Objectives
To ask adrenal tumor researchers and clinicians from the European network for study on adrenal tumors (ENSAT) about the landscape of data management and sharing capacities in the context of legal, information technology and ethical considerations.
Methods
Data collection was performed through a standardized survey with a total of 67 questions sent to 140 clinical and research entities in 36 European countries. All research entities were ENSAT expert clinical and/or research centers. The survey was filled out once by each center, using the SurveyMonkey ® system. Answers were counted as absolute numbers. Percentages were calculated. Comparisons of

answers between inclusiveness target countries (ITC) and non-ITC (as defined by the Cost Action program) were performed using Fisher exact tests.
Results
Seventy-three centers from 34 countries answered the survey. The majority of the surveyed participants use an Electronic Health Record (EHR) system, which is now the main source of data ($n = 66/73, 90\%$). However, significant variability was reported, entailing >35 EHR providers, and variable data collected. Variable stakeholders' implication for enabling data sharing was reported, with more lawyers ($P = 0.023$), patient representatives ($P < 0.001$), ethicists ($P = 0.002$), methodologists ($P = 0.023$) and information technology experts ($P < 0.001$) in non-ITC centers. Globally, implication of information technologies experts for the purpose of data collection and sharing was underwhelming ($n = 24/73, 33\%$). Funding for clinical research was found to be higher in non-ITC than in ITC for clinical trials ($P = 0.01$) and for registry-based and cohort studies ($P = 0.05$). However, for retrospective studies addressing a specific clinical question, the funding was either very low (<10%) or non-existent for both ITC and non-ITC ($n = 22/59, 37\%$ and $27/59, 46\%$ respectively), corresponding to the absence of dedicated support for information technology ($n = 51/59, 86\%$) and ethical and regulatory aspects ($n = 52/59, 88\%$) for these studies.
Conclusions
In the absence of dedicated funding for retrospective research, current requirements for data sharing are obstacles. For the future of data collection on adrenal tumors, retrospective analyses in Europe depend on the capability of academic institutions to provide and standardize sponsorships and agreements, together with the use of simple and versatile information technology tools.

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12

Genetic alterations guide the phenotype of patients with PBMAH: study of 354 index cases

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Objective
Primary bilateral macronodular adrenal hyperplasia (PBMAH) is the most common cause of Cushing's syndrome with bilateral adrenal origin. Pathogenic variants of ARMC5 and KDM1A tumor suppressor genes are causing around 25% of isolated PBMAH cases and variants of PDE11A gene, are frequently associated with the disease, but causality has not been formally established.
Methods
The leukocyte DNA of 354 index cases of PBMAH, from 8 European, American and Brazilian centers, was sequenced for these 3 genes and the phenotype of the patients was analyzed.
Results
In this cohort, 19.2% of patients presented ARMC5 and 2.1% KDM1A pathogenic variants (mutually exclusive) Patients had PDE11A pathogenic variants in 11.4% of cases (similarly distributed in ARMC5-altered and wild-type group). Patients carrying pathogenic variants of ARMC5 and KDM1A presented a severe phenotype, compared to wild-type patients, with a significant increase in urinary free cortisol (UFC) (2.18 and 2.86 vs 0.95 ULN (upper limit of normal), $P = 0.004$) and midnight cortisol (338.9 and 432.85 vs 188.97 nmol/l, $P = 0.004$) as well as more adrenal nodules (10.82 and 6.67 vs 3.45, $P = 5.94$ -7). Patients with pathogenic variants of PDE11A had a phenotype of attenuated severity with lower UFC (0.7 vs 1.25 ULN, $P = 0.0002$), midnight cortisol (157.81 vs 222.19 nmol/l, $P = 0.016$) and number of adrenal nodules (3.46 vs 4.74, $P = 0.048$) than wild-type PDE11A individuals, conferring a phenotypic modulatory role to this gene. Thus, adrenalectomy was performed in 71%, 60% and 37% of patients with pathogenic variants of KDM1A, ARMC5 and PDE11A, respectively. In this cohort, 44 patients (12.5%) underwent bilateral adrenalectomy and 64 patients (18%) unilateral adrenalectomy as a first line treatment, with 13 patients having secondarily a totalization, after unilateral adrenalectomy, because of inefficiency.
Discussion
The strong genotype/phenotype correlation observed in PBMAH encourages monitoring and treatment based on the genetic alterations of patients.

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138

Correlation of biochemical secretion and imaging parameters on [18F]-SiTATE-PET/CT in pheochromocytoma and paraganglioma

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Introduction
Somatostatin receptor (SSTR)-targeted PET/CT is widely used for diagnosing and monitoring pheochromocytoma and paraganglioma (PPGLs). This study aims to evaluate the potential of the novel SSTR-targeted tracer [18F]-SiTATE in diagnosing PPGLs by comparing imaging parameters with tumor marker levels and secretory activity in a small cohort of patients diagnosed with PPGL.
Methods
All patients with histologically confirmed PPGL who presented for [18F]-SiTATE-PET/CT at LMU Klinikum between October 2020 and February 2024, along with hormonal laboratory analysis of both plasma and 24-hour urine samples within up to 100 days, were included. Metabolic tumor volume (MTV) was assessed using a threshold of mean standard uptake value (SUVmean) of 5.0. Total lesion uptake (TLU) was assessed as SUVmean × MTV. Correlation was tested using Spearman's rank correlation test.
Results
Thirty-four out of 39 patients (median age: 55, range: 5-83) were included in this study, with 5 patients with cervical PGL excluded. Twenty-one patients had metastatic disease. There was a moderate correlation between TLU and MTV and urinary dopamine ($r = 0.50$-0.51, $P < 0.05$) as well as norepinephrine ($r = 0.50$-0.54, $P < 0.05$). TLU and MTV also moderately correlated with serum chromogranin-A levels ($r = 0.60$, $P < 0.01$). Additionally, a moderate correlation was found between TLU and MTV with plasma normetanephrine and 3-methoxytyramine ($r = 0.52$-0.56, $P < 0.01$).
Conclusion
MTV and TLU measured with [18F]-SiTATE-PET/CT correlate well with serum chromogranin-A and specific catecholamine pathway biomarkers in urine and plasma, reflecting metabolic tumor activity. Despite the limitations of the relatively small cohort, our results suggest that TLU in [18F]-SiTATE-PET/CT could be used as an imaging biomarker for monitoring disease progression and secretory activity in patients with PPGL.

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80

Prognostic factors influencing survival in patients with metastatic adrenocortical cancer

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Introduction
Despite advancements in the treatment of adrenocortical carcinoma (ACC), the prognosis for metastatic disease remains poor. This study aims to identify prognostic factors for survival in patients with metastatic ACC.
Materials and Methods
This retrospective study included 23 patients with metastatic ACC treated between 2012 and 2023. The main outcomes were overall survival (OS), progression free survival (PFS) and disease specific survival (DSS).

Results
The median age of patients was 60 (IQR 48-67) years, with 80% being female. The median tumor size was 123 mm (IQR102-160), and 18 patients had Cushing syndrome. The liver and lung were the most frequently affected organs (14 and 18 patients, respectively). Fourteen patients underwent adrenalectomy (R2 resection). As the first line medical treatment, among the operated patients, three received mitotane monotherapy, and 11 received mitotane plus platinum-based chemotherapy. In the non-operated group, one patient received mitotane monotherapy, while five others were treated with a combination of mitotane and platinum-based chemotherapy. Three non-operated patients, who received no medical treatment, died within one month of diagnosis. Over a median follow-up of 9 months, (IQR 5-22), 21 patients died, 18 of whom from ACC. The median PFS was 3 months 95% CI (2-4), median OS was 9 months 95% CI (4-14), and median DSS was 9 months 95% CI (6-10). Patients who underwent adrenalectomy had longer OS compared to non-operated patients (18 months vs. 2 months; $P = 0.0132$). In contrast, patients with liver metastases had shorter OS (8 months vs. 22 months, $P = 0.24$) and tended to have shorter DSS (8 months vs. 17 months, $P = 0.063$). The presence of cortisol excess did not influence OS or DSS.
Conclusion
In patients with advanced ACC, the presence of liver metastases was associated with shorter OS. Conversely, surgical removal of the primary tumour was associated with longer OS.

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4

Androgen secreting adrenocortical carcinoma

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Introduction
Adrenocortical carcinoma (ACC) is a rare malignancy with estimated annual incidence of 0,7 to 2 cases per milion, and it is more commonly diagnosed in women. Being extremely agressive entity, survival median of four years is not suprising. Hormone secreting ACC is found in 60% of patients diagnosed with disease, whereas isolated hyperandrogenism is found in 3-5% cases of adult patients.
Case presentation
We present the case of 63-year-old patient who was hospitalized in endocrinology department for functional testing of adrenal incidentaloma. She presented with abdominal pain and fatigue and malaise, clinically she was obese with signs of hyperandrogenemia i.e. marked hirsutism. In laboratory results we found increased values of DHEAS of 1073..1326,2 mg/dl and testosteron: 2,09 ng/ml, while ACTH, daily cortisol, renin, aldosteron and 24h urinary catecholamine values were in refferent range. The Chest CT revealed no abnormalities, while abdominal NMR detected expansive heterogeneous mass with smaller zones of necrosis sized 11 $\times$ 9.4 $\times$ 11.5 cm with suppression of the pancreas but without signs of infiltration of surrounding structures. Abdominal surgeon was consulted, patient was operated on and pathohistology finding showed adrenal cortical carcinoma Fuhrman grade III, pT2, Ki67 $<$5%, ENSAT stage 2. Patient was reffered to higher instance for the decision of whether to introduce adjuvant therapy, which was not instituted at the time. In the further course of treatment, disease recurrence was verified, she was reoperated on and adjuvant mitotane was introduced. Patient died 12 months upon diagnosis.
Conclusion
As already stated, ACC is highly invasive malignancy with poor treatment outcome regardless of therapeutic measures. Further research is needed to assess the best therapeutic modality in recurrent disease.

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158

Adrenocortical carcinoma: new insights from a tunisian cohort

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Introduction
Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with poor prognosis despite diagnostic and therapeutic advances. Tailoring personalized management strategies of ACC in low and middle income countries is hindered by data scarcity. This study aims to specify clinico-biological presentation and therapeutic outcomes of patients with ACC in the context of a developing country.
Methods
We reviewed demographic, clinical, pathology and follow-up data of 11 patients followed for ACC from 2010 to 2022 in a referral endocrine center of the region of Sfax, Tunisia.
Results
Our population was remarkably feminine (8/11 patients) with a mean age at diagnosis of 43 $\pm$3 years. Compression signs and hyperandrogenism were the commonest initial presentation features. Autonomous secretion was present in 7 cases: hyperaldosteronism (3/11), hyperandrogenism (3/11) and hypercortisolism(1/11). ACCs were predominantly right-located and heterogeneous with a mean size of 14,8 $\pm$4 cm. Six patients had metastatic localization at presentation. Mean ENSAT stage at diagnosis was 3$\pm$1 and 7 patients had Weiss score $>$6. Heterozygosity loss of 17p13 was identified in one case. Complete resection was achieved in 6 cases out of 11. Only 7 and 3 patients had adjuvant treatment with mitotane and chemotherapy (EDP protocol) respectively. At 7$\pm$5 years of follow up, relapse rate was 50% and mortality rate 28%.
Conclusion
We meet the epidemiological and clinical profile of ACCs as observed in large Western cohorts. However, we highlight alarming traits specific to our context: diagnostic delay leading to severe presentations with tumor size, cancer stage, and histopathological score significantly more advanced than those reported in the literature, the unavailability of biomolecular study platforms limiting the possibility of personalized management, and limited access to adjuvant therapies due to economic constraints in developing countries. These factors may explain the disappointing therapeutic outcomes and the poorer prognosis of ACCs in our context.

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57

Familial mysteries unraveled: MEN1 and the intricacies of gonosomal mosaicism

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Introduction
Multiple endocrine neoplasia–type 1 (MEN1) is an autosomal dominant cancer syndrome characterized by tumors in at least two of the following: parathyroid, endocrine pancreas, and anterior pituitary. MEN1 mutations may exhibit gonosomal mosaicism— a combination of somatic and germ-line tissue mosaicism. We present a family with gonosomal mosaicism in MEN1.
Case Presentation
A 43-year-old man presented with sudden neck enlargement, type 2 diabetes, hyperuricemia, and a family history of MEN1. His sister has a history of hyperprolactinemia, hypogonadal axis failure, hypothyroidism, and primary hyperparathyroidism, and she was diagnosed with a MEN1 mutation. The patient's neck ultrasound revealed two focal lesions in the left supraclavicular fossa. Thin-needle biopsy showed monomorphic cells with a 'salt and pepper' chromatin pattern and pink cytoplasm. Differential diagnoses included neuroendocrine neoplasm (NEN) or medullary thyroid carcinoma (MTC). Tests indicated primary hyperparathyroidism with elevated IGF-1 and Chromogranin A. Radiological imaging revealed necrotic lymph nodes, chest masses, and pancreatic lesions. Surgical biopsy of a cervical lymph node detected atypical carcinoid (thymic NET G2). The patient received Octreotide, radiation therapy, and Everolimus. Genetic analysis identified a pathogenic MEN1 variant. Considering the MEN1 mutation in both siblings, first-degree relatives were examined. The mutation was absent in the parents' blood despite the dominant inheritance pattern. Consanguinity was confirmed, suggesting parental genetic mosaicism. Analysing DNA from eyebrow hair follicles and cheek swabs (different germ-layer than blood) confirmed the father's gonosomal mosaicism. The patient's father shows no subjective symptoms.

Conclusions
The patient's father should undergo periodic screening for MEN1 spectrum tumors. This case illustrates divergent MEN1 courses in siblings with the same mutation. Genetic testing should be extended to assess the potential spread of the mutation within other relatives. Only one case of gonosomal MEN1 mutation was described - it led to symptomatic disease there. No cases have reported asymptomatic gonosomal mosaicism.

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151

Second neoplasms in patients with sporadic neuroendocrine neoplasms (NENs)

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Introduction
Neuroendocrine neoplasms (NENs) are relatively rare, with an incidence of approximately 0.5 per 100,000 people. This study aims to explore the prevalence of secondary neoplasms in patients diagnosed with sporadic NENs.
Methods
We retrospectively analyzed clinical and histological data from patients treated at our NEN clinic between 2020 and 2023. Patients with known genetic syndromes were excluded from the study.
Results
Fifty patients were evaluated, 60% of whom were women, with ages ranging from 18 to 78 years at diagnosis. Within this group, 17 patients (42.5%) had pancreatic NEN, 7 (17.5%) had small bowel NEN, 7 (17.5%) had gastric NEN, 3 (7.5%) had appendix NEN, 3 (7.5%) had rectal NEN, 2 (5%) had lung NEN, and 1 (2.5%) had duodenal NEN. Among these, 7 tumors (17.5%) were functioning: 3 with carcinoid syndrome, 2 with insulinoma, 1 with VIPoma, and 1 with gastrinoma. For differentiation, 29% of gastroenteropancreatic NENs had a Ki-67 index below 3% (grade 1), 66% had a Ki-67 index between 3-20% (grade 2), 1 patient had neuroendocrine carcinoma, and in 1 patient Ki-67 was unavailable. Twenty-eight secondary neoplasms were found in 22 patients (55%), with 5 patients having multiple secondary neoplasms. The most common were adrenal incidentalomas (9, 32%), meningiomas (3, 11%), and 2 each (7%) of papillary thyroid carcinoma, pancreatic adenocarcinoma, and prostate cancer. Additionally, 3 secondary neoplasms were malignant and 7 were benign. Regarding timing, 10 patients (36%) had synchronous diagnoses, 6 had metachronous diagnoses, and 12 (43%) had NEN diagnoses following another neoplasm. One-fourth of secondary neoplasms were malignant.
Conclusion
Over half of the patients with NENs also had a secondary neoplasm, suggesting a potential genetic link. Further clinical and genetic research is needed to understand these mechanisms.

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143

Decoding allgrove syndrome: a clinical odyssey through diagnosis and management challenges

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Introduction
Triple A syndrome is a rare multisystem autosomal recessive condition, with a classical triad of Alacrimia, achalasia, and adrenal insufficiency. We describe our patient's clinical and genetic profile, highlighting the often-missed diagnosis due to its staggered presentation.
Case presentation
A 22-year-old male, with history of Adrenal insufficiency diagnosed at age 3 and maintained on Glucocorticoid replacement presented to our emergency room in adrenal crisis precipitated by upper respiratory tract infection. At age 3, he was evaluated for hyperpigmentation, failure to gain weight, and muscle weakness, leading to a diagnosis of ACTH-resistant Adrenal insufficiency. He experienced recurrent respiratory infections precipitating adrenal crises. The patient was cachectic, had dysmorphic facies, hyperpigmentation, generalized hyperreflexia, and noticeable intellectual disability. Additionally, he reported regurgitation and vomiting after food intake, and difficulty swallowing liquids since age 5. His parents had observed alacrimia since age 3, noting his increased tolerance to illness and lack of tears. Following stabilization of the adrenal crisis, the patient underwent barium swallow and upper gastrointestinal endoscopy, revealing achalasia cardia. Alacrimia was confirmed by Schirmer's test (2 mm at 5 minutes) in both eyes. These clinical manifestations suggested AAA syndrome, prompting screening for other systemic involvement, revealing borderline intellect (25% disability), bilateral minimal hearing loss, orthostatic hypotension, and reduced cardiac autonomic tone. Genetic analysis confirmed a homozygous missense variant in exon 1 of the AAAS gene: c.43C>A, p.Gln15Lys. Following peroral endoscopic myotomy, his dysphagia and BMI improved. The frequency of respiratory tract infections, which precipitated recurrent adrenal crises, decreased. He is under follow-up and maintained on artificial tears, glucocorticoids, and mineralocorticoids.
Conclusion
Allgrove syndrome is underreported due to its complex, multisystem, and metachronous presentation. Our case emphasizes the need for high index suspicion of this rare syndrome and effective management of various components thereby reducing the catastrophic complications associated with the disease.

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2

Young patient with both ovarian teratoma and adrenal ganglioneuroma

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Introduction
Ovarian dermoid cysts, also known as mature cystic teratomas (MCTs), account for 69% of ovarian embryonal cell tumors in young women. It is a rare type of embryonic cell tumor that can contain immature but also fully formed tissue, including teeth, hair, bones and muscles. Ganglioneuroma is a benign neurogenic tumor. These tumors originate from the neuroepithelium along the sympathetic ganglia. The main localization is the mediastinum.
Case report
We present the case of a 27-year-old female patient with a large intra-abdominal tumor mass, which after surgical removal was pathohistologically proven to be a mature ovarian teratoma. One year after the operation, a diagnostic procedure was performed to test the functionality of the tumor of the right adrenal gland. After the indicated surgical intervention, it was proved pathohistologically that it was an adrenal ganglioneuroma. The simultaneous presentation of such two very rare tumors represents a kind of rarity.

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163

Osilodrostat as a safe and effective treatment for cushing disease in adolescent patient

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Osilodrostat as an inhibitor of adrenal 11B-hydroxylas, is an effective medication used in the management of endogenous hypercortisolism. There are limited data regarding usage of osilodrostat in adolescent patients. Case presents a 16-year-old female who was admitted to Endocrinology Department due to suspicion of Cushing Syndrome. Patient's medical history was significant for newly diagnosed hypertension, diabetes mellitus type 2, menstrual irregularities, insomnia for few months. Physical examination was prominent for obesity (BMI 37 kg/m^2), acanthosis nigricans, red striae, buffalo hump, face plethora. Hormonal evaluation indicated ACTH dependent Cushing Syndrome. It showed impaired cortisol circadian rhythm (serum morning cortisol: 15.5 mg/dl, serum midnight cortisol 15 mg/dl), elevated ACTH level (146 pg/ml), elevated late night salivary cortisol

(2.7 × ULN), elevated urinary free cortisol (2.8 × ULN). Desmopressin test showed cortisol rise by 25% and ACTH rise by 69%. Pituitary MRI visualized microadenoma. Additional laboratory evaluations showed uncontrolled diabetes mellitus (HBA1C 7.10%), elevated liver enzymes (ALT 7 × ULN, GGTP 3 × ULN, ALP 1.7 ULN). Abdominal USG showed liver steatosis. Densitometry indicated normal bone density. Osilodrostat treatment was introduced with initial daily dosage of 2 mg, followed by titration to 5 mg daily with good clinical tolerance. The dosing was adjusted based on cortisol level in urine, late night cortisol in saliva, patient's clinical symptoms. During 2 months of treatment with osilodrostat, patient showed biochemical (normalization of late-night saliva cortisol and urinary free cortisol) and clinical control (better control of diabetes mellitus and hypertension, sleep pattern normalization, 4% weight loss). After initial preparation with osilodrostat, patient is planned to undergo transsphenoidal pituitary adenoma removal. Clinical trials of osilodrostat in children and adolescents are lacking. This case describes its potential role in these populations.

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22

Primary aldosteronism: small molecule antagonists of mutant KCNJ5 potassium channels

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Introduction
Major advances have been made in understanding the pathophysiology of primary aldosteronism (PA). A breakthrough was the identification of mutations in the potassium channel KCNJ5, which drive aldosterone overproduction in aldosterone-producing adenomas and familial hyperaldosteronism type III. Our objective was to identify small molecules that selectively target mutated KCNJ5 channels to broaden the therapeutic strategies for PA.
Methods
We conducted a virtual screening of over 6 million small molecules to identify those that potentially bind to KCNJ5 channels. The functionality of these candidate molecules was evaluated *in vitro* using human adrenocortical cells. Assessment included cell viability assays, flow cytometry, confocal microscopy, qPCR, and mass spectrometry for steroid measurements.
Results
The virtual screening identified 108 candidate molecules. Each was tested for antagonist activity by evaluating their ability to rescue mutant KCNJ5-induced cell death. A positive correlation was observed between multiple aromatic rings in the candidate compounds and increased cell death rescue. Among these molecules, compound-81 (C-81), effectively rescued adrenal cell death induced by mutated KCNJ5 in both monolayer and spheroid cultures. The specificity of C-81 for mutated vs. wild-type KCNJ5 was demonstrated by a reduction in aldosterone synthase (CYP11B2) gene expression induced by different KCNJ5 mutations (69% - 88% reduction for KCNJ5 L168R, T158A, and G151R), with negligible effects on angiotensin II-stimulated CYP11B2 expression in unmutated cells. Consistently, C-81 led to a 73% decrease in aldosterone secretion from cells expressing KCNJ5-L168R without significantly affecting cells overexpressing wild-type KCNJ5. Mutated KCNJ5 substantially increased cortisol production, while C-81 treatment reduced cortisol secretion by 75%.
Conclusion
High-throughput virtual screening is a valid approach for the discovery of novel therapeutics that selectively target aldosterone overproduction driven by a KCNJ5 mutation. C-81 or its structural analogs are putative small molecule antagonists targeting pathological aldosterone secretion in both sporadic and familial forms of PA.

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72

The imaging and biochemical characteristics of pheochromocytoma

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Introduction
The majority the pheochromocytomas (PCCs) are diagnosed incidentally. The absence of characteristic paroxysmal symptoms does not exclude the diagnosis. The purpose of this study is to evaluate the diagnostic sensitivity of imaging features and biochemical markers in PCCs, providing data to improve clinical decision-making.
Methods
The available imaging results, clinical and biochemical data of patients who underwent laparoscopic adrenalectomy at our institution from January 2015 to May 2024 with histopathological diagnosis of PCC were collected and retrospectively analyzed. The sensitivity of imaging features was calculated based on the available results, and not all patients had information regarding every specific feature.
Results
Among 52 patients (52% female) included, 92% were primarily diagnosed with adrenal incidentaloma. 2 patients were diagnosed with bilateral PCCs. Radiologic anatomical examinations included computed tomography (CT) and/or magnetic resonance imaging (MRI) revealing a median tumor size of 38.5 mm (range 15-82 mm). On CT scans lesions had attenuation of >10 HU (median 33 HU; range 15-50 HU) or were heterogeneous. Median enhancement in portal venous phase was 72.5 HU (range 37-170 HU). The sensitivity of an absolute wash-out $<60\%$ was 91% (20/22). Additional features were heterogeneous enhancement after contrast and cystic/necrotic components with sensitivity of 32% (16/50), respectively. Key findings on MRI scans included heterogeneity (sensitivity of 50%, 14/28), no loss of signal in T1 out-of-phase sequence (39%, 11/28), heterogenous and elevated enhancement after contrast (36%, 10/28 and 39%, 11/28, respectively), restricted diffusion (46%, 13/28), cystic component (39%, 11/28), and high signal on T2 (14%, 4/28). Elevated metanephrine and normetanephrine in urine correlated with lesion size. Normetanephrine showed higher sensitivity (87.0%) than metanephrine (60.9%), with a tendency of predomination of one of the metabolites.
Conclusion
The diagnosis of pheochromocytoma must be based on a comprehensive analysis of the imaging findings. Features indicating heterogeneity and cystic or necrotic components in correlation with biochemical data are crucial for optimizing treatment planning, including surgical intervention.

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42

A case of cushing's syndrome in pregnancy – a story of frequent misdiagnosis

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Introduction
Cushing's syndrome (CS) is a condition characterized by chronic exposure to excess glucocorticoids, mostly due to adrenocorticotropic hormone (ACTH) excess, but in 10–15% due to ACTH-independent cortisol excess. Although CS directly or indirectly affects most organ systems, there can often be a significant diagnostic delay, especially during pregnancy.
Case presentation
Twenty-nine-year-old woman complaining about pain in her lower back, high blood pressure, swelling of lower extremities and nausea was admitted because of newly discovered mass of right adrenal gland. She had a C-section 5 months before admission in her 32nd week of pregnancy because of preeclampsia and diabetes. The patient has had diabetes since her 2nd month of pregnancy and has been using slow-acting insulin ever since. She was diagnosed with hypertension during pregnancy, with high blood pressure even after delivery. One month after delivery, patient started experiencing pain in thoracolumbar spine, X-ray showed fractures of L3 and L4 vertebrae. Computed tomography and magnetic resonance imaging showed reduced bone mineral density, multiple compressive fractures of thoracolumbar spine, and a heterodense right adrenal mass, 47×25 mm in diameter. During physical exam, moon face and purple stretch marks on her lower abdomen and thighs were seen. Endocrinological examination revealed elevated

basal cortisol without circadian rhythm, and low ACTH. Overnight dexamethasone suppression test, low-dose and high-dose dexamethasone suppression tests were without cortisol suppression. After preoperative preparation, right-sided adrenalectomy was performed. Glycemic profiles and HbA1c after surgery were normal and antidiabetic therapy was stopped. She also remained normotensive with normal cortisol, ACTH, and electrolyte status. Pathohistological examination confirmed adrenal adenoma.

Conclusion

The diagnosis of CS in pregnancy is often delayed because symptoms overlap with the changes associated with a normal pregnancy. Increased awareness of CS, especially during pregnancy, is necessary, as CS can affect maternal and fetal outcomes.

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111

Endocrine disrupting chemicals and altered gluco- and mineralocorticoid hormone levels – a systematic review of epidemiological studies

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Background

The role of endocrine disrupting chemicals (EDCs) in the development of the metabolic syndrome and its components gained increasing importance in recent years. The underlying mechanisms appear to be multifactorial and are largely unresolved. Disruption of glucocorticoid and mineralocorticoid hormone action is considered a possible mechanism. This systematic review is the first to summarize epidemiological studies investigating an association between EDC concentrations and altered levels of glucocorticoids, mineralocorticoids, and ACTH.

Methods

Following the PRISMA guidelines, we searched PubMed (n = 2,039) and the Cochrane Library (n = 55) for epidemiological studies published until 1st April 2024 without restrictions on the age, geographic origin and sex of the study population. Various groups of EDCs were evaluated with the prerequisite of direct measurement of the chemical, a metabolite, or biomarker.

Results

We identified 2,094 articles. After removing duplicates and screening, 27 studies were included. Fifteen studies investigated children; five studies examined pregnant women. Studies focused predominantly on glucocorticoids (n = 26) compared to mineralocorticoids (n = 5) and ACTH (n = 2). The most studied EDCs were pesticides (n = 9) and phthalates (n = 8), followed by per- and polyfluoroalkyl substances (PFAS, n = 6), other persistent organic pollutants (POPs, n = 6), and bisphenols (n = 5). All but three studies demonstrated a significant association between the concentration of specific EDCs and hormone levels, although results varied depending on the chemical and its metabolites, and sex and age of the study population.

Conclusion

There is compelling evidence for the impact of specific EDCs on plasma glucocorticoid and mineralocorticoid concentrations in different age groups worldwide. Further research combining EDC concentration, hormone levels and clinical features, complemented by experimental investigations to study cell mechanisms, is needed to gain holistic knowledge of EDCs influence on corticosteroid-related disorders.

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Calcium and Bone

47

A case report of severe osteomalacia in a young adult female - in search of a FGF23 secreting tumor

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Introduction
Tumor-induced osteomalacia (TIO), is a rare paraneoplastic syndrome caused by mesenchymal tumors which are typically benign, small and slow-growing. They express and secrete fibroblast growth factor 23 (FGF23), leading to decreased reabsorption of phosphate and production of 1,25-dihydroxyvitamin D by the kidney. The resulting hypophosphatemia causes osteomalacia, bone pain, muscle weakness, and fractures.
Case presentation
This is the case of a 50 year old woman, referred to our department with a long history of diffuse bone pain and progressive muscle weakness, which finally led to the impossibility of walking without support. She associated vertebral osteosclerosis with spinal disc herniation and spinal stenosis from the age of 44, as well as multiple fragility fractures of the vertebrae, hips, femur, ribs and even scapula due to hypophosphatemic osteomalacia. FGF 23 levels were elevated, along with low serum phosphate, normal vitamin D, and normal serum calcium which implied necessary finding the secreting tumor. Multiple imagistic techniques were used in the attempt of localizing the source (repeated CTs, 18F-FDG PET-CT) with no specific results. Five years after the onset of symptoms, a tumor was localized in the left ethmoidal region of the skull using Tektrotyd scintigraphy followed by cerebral MRI. Excision of the tumor led to normalization of FGF-23 and phosphate levels, as well as complete resolution of all musculoskeletal symptoms.
Conclusion
TIO is a rare syndrome with non specific symptoms, which is often misdiagnosed with a variety of skeletal, rheumatologic or neuro-psychiatric diseases, leading to a significant decrease in quality of life and severe functional impairment, as we can see in our patient. FGF23 secreting tumors are difficult to find, therefore definitive treatment is delayed. These facts highlight the importance of considering TIO and including the measurement of serum phosphate in any patient with fractures, persistent bone pain and muscle weakness.

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70

Bone-active drugs in pre-menopausal women with breast cancer undergoing hormone deprivation therapies

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Background
Bone health management in pre-menopausal women with breast cancer (BC) under hormone-deprivation therapies (HDTs) is often challenging, and the effectiveness of bone-active drugs is still unknown.
Methods
This retrospective multicenter study included 306 premenopausal women with early BC undergoing HDTs. Bone mineral density (BMD) and morphometric vertebral fractures (VFs) were assessed 12 months after HDTs initiation and then after at least 24 months.
Results
After initial assessment, bone-active drugs were prescribed in 77.5% of women (151 denosumab 60 mg/6 months, 86 bisphosphonates). After 47.0 ± 20.1 months, new VFs were found in 16 women (5.2%). VFs risk was significantly associated with obesity [OR 3.87, $P = 0.028$], family history of hip fractures or VFs (OR 3.21, $P = 0.040$], chemotherapy-induced menopause (OR 6.48, $P < 0.001$), pre-existing VFs (OR 25.36, $P < 0.001$), baseline T-score $\leq$-2.5 SD at any skeletal site (OR 4.14, $P = 0.036$) and changes at lumbar and total hip BMD (OR 0.94, $P = 0.038$ and OR 0.88, $P < 0.001$, respectively). New VFs occurred more frequently in women untreated compared to those treated with bone-active drugs (14/69, 20.8% vs. 2/237, 0.8%; $P < 0.001$) and the anti-fracture effectiveness remained significant after correction for BMI (OR 0.033; $P < 0.001$), family history of fractures (OR 0.030; $P < 0.001$), chemotherapy-induced menopause (OR 0.04; $P < 0.001$) and pre-existing VFs (OR 0.014; $P < 0.001$).
Conclusions
Pre-menopausal women under HDTs are at high risk of VFs in relationship with high BMI, densitometric diagnosis of osteoporosis, pre-existing VFs and family history of osteoporotic fractures. VFs in this setting might be effectively prevented by bisphosphonates or denosumab.

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67

Abstract withdrawn

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34

Male osteoporosis, a still overlooked and undermanaged issue: an identikit of patients seeking bone health evaluation at a tertiary academic medical centre

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Introduction
Male osteoporosis is undermanaged. The aim of this study was to characterize from real-life data male patients seeking the first bone health evaluation at a tertiary academic medical center, over a 14-year observation period.
Methods
Retrospective, cross-sectional study, including adult men referring to our Center from 2007 to 2021 for bone health evaluation. Comorbidities and history of fragility fractures were investigated. Osteoporosis was defined according to WHO and ISCD criteria.
Results
536 men were included: 74 aged 18-40 years, 73 aged 40-50, 88 aged 50-60, 122 aged 60-70, 128 aged 70-80, and 47 aged $>$80. Prevalence of osteoporosis, osteopenia, and low bone mineral density for age were 42.3%, 44.8% and 48.6%, respectively. 219 patients (40.9%) were affected from at least one comorbidity associated with bone loss and 197 (36.8%) had an endocrinological/andrological diseases that increase fracture risk. At least one fragility fracture has already occurred in 216 patients (40.8%). Sites of fracture were lumbar spine (72.7%), femoral neck alone or in combination with other sites (7.3%). 181 men (33.8%) have never been treated with any anti-osteoporotic therapy, including calcium and vitamin D. Most of fractured patients underwent bone specialist’s consultation only once fragility fractures have occurred.

Conclusions
Male osteoporosis presents with a high rate of fragility fractures among men referring to a tertiary academic medical center. The high prevalence of comorbidities associated with bone loss suggests that secondary forms of osteoporosis prevail in men, and they should be carefully investigated to identify patients at increased fracture risk. Most of fractured patients have not been previously evaluated by a bone specialist or properly treated, suggesting that awareness for male osteoporosis needs to be reinforced in primary healthcare setting. This disease remains still overlooked.

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149

Bone suffering in 'tertiary' hyperparathyroidism - from generalized brown tumors to hungry bone syndrome

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Introduction
Tertiary hyperparathyroidism (tHPT) develops when the parathyroid gland becomes autonomous in hormone secretion, usually after prolonged secondary hyperparathyroidism. "Brown tumours" (BT) and postoperatively "hungry bone syndrome" (HBS) are rare complications of HPT occurring in up to 1.5% in tHPT and around 13% in primary HPT, respectively.
Case presentation
A 49-year-old female patient was referred to an endocrinologist due to hypercalcemia. Among clinical findings, the patient is obese and has cutaneous calcifications. Examinations started 2 years before, because of gradually increasing bone pain. She was then diagnosed with chronic kidney disease (stage IV/V) and dilated cardiomyopathy. There was clinical suspicion of multiple myeloma or metastatic disease. CT scan showed osteolytic lesions in both scapula, IV-IX ribs, VIII and IX vertebrae, pelvic bones and femur. During the evaluation, we found hypercalcemia (corrected calcium 2.5-2.85 mmol/l) with hypocalciuria, hypovitaminosis D, elevated alkaline phosphatase, hyperparathyroidism (PTH 1160-1267 ng/l) and high bone turnover markers. Osteodensitometry showed osteoporosis. Neck ultrasound revealed a hypoechogenic mass left paratracheal measuring 10 x 23 mm, and MIBI scintigraphy confirmed hyperactive left inferior parathyroid. A total parathyroidectomy was performed, revealing a left inferior parathyroid adenoma. Postoperatively PTH was 58-80 ng/l, and profound hypocalcemia (corrected calcium 1.4-1.8 mmol/l) was observed. Continuous intravenous calcium gluconate therapy alone lasted for 2 weeks, following high-dose of oral calcium carbonate (up to 16 g/24h) and calcitriol (up to 3 mg/24h) in combination with calcium gluconate intermittent boluses. She was discharged with 12 g/24h calcium carbonate and 2 mg/24h calcitriol, and with careful control of biochemics, the dose was reduced.
Conclusion
BT should be suspected in patients with chronic kidney disease complicated with tHPT, as it can easily be mimicked by multiple myeloma and tumour metastasis (our patient's case raised clinical doubt between primary HPT and tHPT). HBS should be kept in mind postoperatively, especially in patients with generalized BT and longstanding HPT.

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164

Bone mineral density in multiple endocrine neoplasia ten years after primary parathyroidectomy

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Introduction
Primary hyperparathyroidism (PHPT) associated with multiple endocrine neoplasia type 1 (MEN1) impairs bone mineral density and causes ostoporosis already in young patients. We aimed to investigate BMD in a contemporary cohort of patients with MEN1-related PHPT after long term follow-up and compare these results to that of healthy controls.
Methods
Thirty-five patients with genetically confirmed MEN1 were diagnosed with MEN1 at mean age 28.7 +/- 13.6 yrs. Thirty-two (91.4%) underwent primary parathyroidectomy at mean age 33.3 +/- 13.7 yrs, twelve had undergone at least two surgeries with on average 7.3 +/- 5.9 yrs between the operations. BMD was assessed by DXA at the end of mean follow-up, 13.2 yrs after the primary parathyroidectomy and compared to that of 35 age- and gender-matched controls. At the time of DXA, 22 patients (62.9%) had mild persistent hyperparathyroidism (mean serum ionized calcium 1.38 +/- 0.06 mmol/l), seven (20.0%) received medication for postoperative hypoparathyroidism.
Results
At mean age of 42.8 +/- 15.7 yrs, T- and Z-scores in lumbar spine, femoral neck and total hip were all within reference ranges. Absolute BMD values in MEN1 patients compared to controls in the lumbar spine, femoral neck and total hip were 0.986 +/- 0.123 vs 1.172 +/- 0.139 g/cm^2 ($P < 0.001$), 0.782 +/- 0.119 vs 0.967 +/- 0.129 g/cm^2 ($P < 0.001$) and 0.931 +/- 0.130 vs 1.022 +/- 0.128 g/cm^2 ($P = 0.004$), respectively.
Conclusion
More than 10 yrs after the first parathyroidectomy, mean BMD in patients with MEN1 is in the normal range. However, it is still significantly lower compared to healthy controls.

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9

Severe osteoporosis in young vegan women with cerebral palsy – a case report

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Introduction
Osteoporosis is a health problem that causes low bone density and quality. Additionally, a high fracture risk is linked with osteoporosis. While it is most commonly associated with postmenopausal women and the elderly, it can also impact individuals with early-onset physical limitations such as cerebral palsy (CP). This study highlights the challenges of managing osteoporosis in a young women with CP.
Case presentation
A 38-year-old woman presented with recent low extremity fractures and a history of frequent rib fractures. She has had multiple risk factors for developing osteoporosis. Dual-energy X-ray absorptiometry (DXA) showed severe osteoporosis with a heightened risk of developing new fractures over the next decade. She rejected medical advice to make changes in her lifestyle and undergo other therapeutic procedures.
Conclusion
Due to multiple condition-related factors, individuals with CP are more likely to suffer from osteoporosis. Our patient's history demonstrates the difficulties in diagnosing and managing osteoporosis in this population. A multidisciplinary approach is necessary to improve outcomes, with an emphasis on lifestyle changes and higher patient adherence. Additional guidelines are needed to improve diagnostic strategies and treatment protocols for this vunerable population.

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157

Associations between serum adipokines and osteoporosis in postmenopausal women: a systematic review

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Introduction
The relationship between adipokines and bone mineral density (BMD) is unclear, with conflicting results.
Objectives
This study aimed to determine if adipokine levels differ between postmenopausal women with osteoporosis and healthy postmenopausal women, and if these levels are associated with low BMD. The adipokines studied included adiponectin, leptin, resistin, visfatin, vaspin, chemerin, omentin-1, retinol binding protein 4 (RBP-4), CTRP3.
Materials and methods
A literature review was conducted using Ovid MEDLINE(R) and Scopus databases from 1946 to 26 July 2019 with updates in November 2020 and July 2023. Postmenopausal women with dual-energy X-ray absorptiometry (DXA) scans and at least one adipokine measurement were included. Osteoporosis was considered if the T score was -2.5 SD or below. If the T score was reported between +1 and -1 SD, subjects were considered to have a normal BMD. Quality assessment was performed using the Joanna Briggs critical appraisal tool. The study protocol was registered with PROSPERO (CRD42020148001).
Results
The research strategy identified 1273 records of which 26 studies were included in this systematic review. Additionally, 3 studies were manually added, making 29 studies in total with a sample size of 3237 postmenopausal women. Most studies were cross-sectional ($n = 26$) with 3 being longitudinal. The studies exhibited a wide heterogeneity in adipokines, sample size, subject characteristics, and BMD measurement site. Leptin and adiponectin were the most frequently studied adipokines. Leptin levels were typically lower in postmenopausal women with osteoporosis, while adiponectin, resistin, chemerin levels were higher. No significant associations were found for other adipokines with osteoporotic status. Most studies showed a positive relationship between leptin and BMD, but no strong evidence supported a link between BMD and other adipokines.
Conclusions
Leptin, adiponectin, resistin and chemerin appear to have a discriminative capacity of osteoporotic status, however, only leptin is consistently associated with BMD.

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114

Unraveling the puzzle of bone health in Klinefelter syndrome: association between dxa derived bone quality indexes and body composition parameters in a single center cohort

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Introduction
Bone mineral density (BMD) lacks sensitivity in individual fracture risk assessment in patients with Klinefelter syndrome (KS), independently of testosterone replacement therapy (TRT). Thus, new dual-energy X-ray absorptiometry (DXA) derived diagnostic tools are needed.
Methods
Trabecular bone score (TBS), bone strain index (BSI) and total body DXA parameters of bone geometry and body composition were evaluated in a single center cohort of men with KS.
Results
44 males with 47, XXY KS were enrolled, with median age 39.5 years (range 18-61). 39/44 (88.6%) patients were receiving TRT, with a median treatment duration of 6.5 years (range 1-37). Median body mass index was 25.4 kg/m^2 (range 17.3-40). Low BMD was found in 7/44 (15.9%) patients. Correlation analysis showed that fat mass index (FMI: r 0.64, $P < 0.001$), fat-to-lean mass index ratio (FMI/lMI: r 0.66, $P < 0.001$) and visceral fat mass (r 0.56, $P < 0.001$) were significantly associated with lumbar BSI. Interestingly, a strong correlation of TBS with lumbar BSI (r -0.73, $P < 0.001$) was also observed.
Conclusion
These single cohort results suggest a possible role of higher body fat indexes as determinants of lower bone quality in adults with KS. Large-scale prospective cohort studies are needed to investigate the predictive value of body composition parameters on fracture risk in KS patients.

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Diabetes, Obesity and Metabolism

30

Relation between autonomic symptoms and CAN risk score in type 2 diabetes: preliminary results

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Introduction
COMPASS 31 questionnaire is widely employed for screening of cardiac autonomic neuropathy (CAN) in diabetes, yet its diagnostic performance varies across studies. The aims of the study are to evaluate the relation between score of the COMPASS 31 and CAN Risk Score in type 2 diabetes (T2D); additionally, to assess its performance in diagnosing diabetic peripheral neuropathy (DPN).
Methods
The study involved 68 participants with T2D (mean age 62.53 ± 10.82 years, duration diabetes 9.87 ± 7.45 years, HbA1c 56.62 ± 14.51 mmol/mol, 76,5% males), so far. All participants underwent DPN assessment, orthostatic hypotension (OH) test, and completed the COMPASS 31. DPN was defined by at least one abnormality among neuropathic symptoms (Michigan Neuropathy Screening Instrument-Q, MNSI-Q) and signs (Diabetic Neuropathy Index, DNI and Michigan Diabetic Neuropathy Score, MDNS). COMPASS 31 was analysed to obtain six domain weighted scores and a total weighted score (TWS), which was considered abnormal if >16.44. CAN risk score was calculated.
Results
In the total cohort, 45.6% of significant TWS of COMPASS 31 and 37.5% of high CAN risk score have been detected. Moreover, DPN prevalence was 42.6%. The TWS was similar in subjects with low and high CAN risk score (15.84 ± 11.19 vs 18.32 ± 11.71.83; *P* 0.648). Considering domains separately, patients at high risk for CAN showed greater impairment in the vasomotor domain (0.29 ± 0.74 vs 0.62 ± 1.16; *P* 0.005) and strongly correlation with secretomotor domain (rho = 0.252, $P = 0.044$); no differences in the weighted scores of the other domains were found. No correlations between TWS and value of OH and CAN risk score were observed. On the other hand, correlations between MNSI-Q and TWS (rho = 0.356, $P = 0.033$) and MNSI-Q and vasomotor domain (rho = 0.90, $P = 0.001$) have been observed.
Conclusion
In these preliminary results, COMPASS 31 exhibits a scarce association with CAN Risk Score in T2D. In contrast, a fair correlation with clinical DPN was observed.

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60

Liver fibrosis and peripheral neuropathy in type 2 diabetes: an observational cross-sectional study

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Background
Hepatic steatosis and diabetic peripheral neuropathy (DPN) share etiological and clinical correlates, while relationship between liver fibrosis and DPN has not been well investigated. AIMS. To evaluate the association between liver fibrosis and DPN and investigate the non-invasive scores of fibrosis as predictors of DPN.
Methods
Observational, cross-sectional study including individuals with type 2 diabetes (T2D) and steatosis. Neurological assessment was performed with Michigan Neuropathy Screening Instrument-Q (MNSI-Q), Michigan Diabetic Neuropathy Score (MDNS) and Diabetic Neuropathy Index (DNI). Fibrosis risk was estimated using Fibrosis-4 (FIB-4), NAFLD Fibrosis Score (NFS), AST/ALT ratio, and AST to platelet ratio index (APRI). Finally, fibrosis was defined by liver stiffness measurement (LSM) $\geq$7.0 kiloPascals (kPa) at Fibroscan.
Results
Eighty-six T2D subjects (mean age 59.22 ± 13.18 years, diabetes duration 9.61 ± 8.87 years, HbA1c 57.71 ± 14.28 mmol/mol, 69.8% males) were included. DPN was detected in 43% of the cohort. Higher FIB-4 and AST/ALT scores were detected in subjects with DPN compared to those without DPN (FIB-4 1.63 ± 0.85 vs 1.23 ± 0.66, *P* 0.018; AST/ALT 1.11 ± 0.61 vs 0.89 ± 0.23, *P* 0.026). Moreover, the DPN group showed higher LSM (7.12 ± 3.58 kPa vs 6.56 ± 4.23 kPa, *P* 0.619) and the MDNS score was correlated with LSM (Rho 0.304, *P* 0.026). At neurological examination, a higher prevalence of alteration was observed in vibration by diapason or reflexes in subjects with fibrosis compared to LSM < 7 kPa (*P* 0.025 and *P* 0.042, respectively). Finally, a qualitative evaluation of vibration or reflexes in individuals with high FIB-4 and/or AST/ALT indexes was associated with DPN (FIB-4 + vibration: *P* 0.047; FIB-4 + reflex: *P* 0.013; AST/ALT + vibration: $P < 0.001$; AST/ALT + reflex: $P < 0.001$).
Conclusions
Exploring easy-to-apply screening methods, the qualitative evaluation of vibration or reflexes would appear effective in identifying DPN in T2D with steatosis.

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21

Differential expression of miRNAs in type 1 diabetes patients: influence of age, diagnosis, body composition, and biochemical parameters

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Introduction
Type 1 diabetes mellitus (T1DM) is an autoimmune disease primarily characterized by the destruction of pancreatic beta cells, leading to deficiencies in insulin production. The development of T1DM is attributed to a combination of environmental, immunological, metabolic, and epigenetic factors. The aim of this study is to analyze the expression profile of circulating miRNAs in T1DM patients to establish differences based on the time of diagnosis, whether in adulthood (AD) or childhood (CD).
Methods
To conduct this study, plasma was collected from individuals with T1DM (30 AD > 14 years and 30 CD < 14 years), as well as from 25 controls. Differentially expressed miRNAs between the groups were selected using NGS sequencing. These results were validated by RT-qPCR and statistically analyzed, along with the demographic data of the participants.
Results
By analyzing the differential expression levels of 7 circulating miRNAs in plasma, statistically significant differences were found in the expression of hsa-miR-340-5p ($P = 0.039$) and hsa-miR-200a-3p ($P = 0.016$) in the T1DM group compared to the controls. Otherwise, when stratified the cohort based on diagnosis age, differences were only found in hsa-miR-200a-3p in the CD group vs the control group ($P = 0.011$). Moreover, correlations between miRNA expression and biochemical and anthropometric parameters were established. A positive correlation was observed between the expression of hsa-miR-224-5p and HDL ($P < 0.001$), and hsa-miR-200a-3p and HbA1c ($P < 0.01$). Finally, negative correlations were observed between hsa-miR-224-5p and hsa-miR-200b-3p and weight ($P < 0.05$) as well as between hsa-miR-340-5p and body fat percentage ($P < 0.05$).
Conclusion
A differential expression of the studied miRNAs was observed in the cohort, which is associated with biochemical and anthropometric parameters. Future studies are needed to determine their relationship with other comorbidities.

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8

Effects of semaglutide, peptide YY3-36 and empagliflozin on metabolic dysfunctionsassociated fatty steatotic liver disease in diet-induced obese rats with chronic nitric oxide synthase-inhibition

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Introduction
Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common comorbidity of obesity. In this study, we sought to determine hepatic metabolic and mitochondrial effects of the Glucagon-like Peptide-1-agonist semaglutide, the sodium-glucose linked transporter 2-inhibitor empagliflozin and Peptide YY3-36 in diet-induced obese rats with additional chronic inhibition of nitric oxide synthase via Nω-nitro-L-arginine methyl ester (L-NAME), to induce accelerated liver injury.
Methods
Following an eight-week feeding period with a high-fat/fructose-diet (HFD) and L-NAME, male wistar rats were randomized into the following treatment groups: semaglutide, empagliflozin, PYY3-36, semaglutide in combination with empagliflozin or PYY3-36 and saline control. After additional 8 weeks, qRT-PCR and WesternBlot was performed to quantify hepatic mRNA and protein expression of metabolic and inflammatory marker genes. Moreover, mitochondrial respiration and redox status was examined using an Oroboros O2K-Respirometer.
Results
In the liver, the de-novo lipogenesis regulating genes mlXIPL and SREBF-1 were downregulated in the semaglutide and PYY3-36 -mono groups and significantly lower in the semaglutide + PYY3-36 group ($P < 0.05$) compared to saline treated controls. In the semaglutide + empagliflozin treated group, mRNA levels of IL-1b and TNF-alpha-levels were lower compared to saline. Regarding mitochondrial respiration, fatty acid-dependent state 3 respiration, empagliflozin ($P < 0.001$) as well as semaglutide + empagliflozin ($P < 0.05$) decreased O2-consumption significantly in comparison to controls. In uncoupled states, empagliflozin and PYY3-36 mono-treatment decreased the O2-rate significantly ($P < 0.05$) compared to saline control. Moreover, semaglutide in combination with PYY3-36 lowered O2-consumption and significantly reduced peroxide-production ($P < 0.01$).
Conclusion
n summary, the presented data indicate a strong improvement of the MASLD. O2-consumption of the respiratory chain in mitochondria is decreased in semaglutide, PYY3-36, and empagliflozin treated rats, supposing reduced metabolic stress in these groups. The strongest effect was detected in semaglutide + PYY3-36 treated animals, which points towards PYY3-36 as a promising additive substance in the treatment of MASLD.

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17

The characteristics of 541 severe hypoglycaemia's presentation and management underscore the need for improved services: pilot data from DEKODE hypoglycaemia study

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Introduction
Clinically significant hypoglycaemia, defined by blood glucose levels below 3 mmol/l (level 2) or requiring third-party assistance (level 3), poses significant risks for individuals with diabetes. However, limited information exists regarding their characteristics, management, and outcomes. The objective was to explore the characteristics, precipitating factors, and outcomes of individuals admitted with level 2 or 3 hypoglycaemia.
Methods
This retrospective study was conducted from October 2023 to January 2024 across 5 UK hospitals, including all adults (>18 years) admitted with level 2 or 3 hypoglycaemia from November 2022 to October 2023. Data on sociodemographics, precipitating factors, management and outcomes were collected. The Charlson comorbidity index (CCI) and clinical frailty score (CFS) were calculated to determine the 10-year survival prognosis and frailty, respectively.
Results
The study included 541 severe hypoglycaemic episodes; 237 in type 1 diabetes and 304 in type 2 diabetes. 441 episodes were level 2, and 100 were level 3. Glucagon was administered in 43 episodes. Median age, CCI, and CFS were 75.0 years, 6, and 6, respectively. Fasting/missed meals (48.8%) and intercurrent illness (14.4%) were common triggers. Hypoglycaemia was unclear in 22.2% of episodes. Cognitive impairment occurred in 24.1%, with 1.48% associated with death during hospitalisation. Insulin dose was reduced in 217 episodes and stopped in 32. Specialist referral post-discharge occurred in 146 episodes, with 20 initiating continuous glucose monitoring. Glucagon prescription at discharge was rare (5/541).
Conclusion
Individuals hospitalised for severe hypoglycaemia were typically elderly and frail, often due to missed meals or intercurrent illness. Despite risks of cognitive impairment and death, services to prevent future episodes were under-utilised. This highlights the need for targeted educational interventions to mitigate such occurrences and improve patient outcomes.

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96

Association between glycemic control parameters and diabetic macular edema in type 1 diabetes: a retrospective study using CGM data

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Introduction
Diabetic macular edema (DME) is one of the leading causes of visual impairment in individuals with diabetes. In type 1 diabetes (T1D), DME is often a late-stage complication of diabetic retinopathy (DR). However, literature remains scarce regarding risk factors for DME, particularly its relationship with glycemic control assessed by continuous glucose monitoring (CGM).
Methods
We conducted a retrospective cohort study of adult T1D patients using Freestyle Libre® CGM, who were followed at a tertiary diabetes and ophthalmology center between January 2022 and June 2024. Exclusion criteria included incomplete ophthalmological evaluations or <70% active CGM usage. Clinical and analytical variables were compared according to DME history. Logistic regression models adjusted for age and sex were performed to evaluate associations between CGM parameters and DME history.
Results
We included 110 patients, with 55% female, mean age of 45.8 ± 12.7 years and T1D duration of 26.8 ± 10.7 years. Sixty-two percent had DR. The average glycated hemoglobin (HbA1c) was 7.8 ± 1.3%, and the mean time in range was 54.8 ± 18.1%. Twenty-one percent had a history of DME, which developed after a mean T1D duration of 25.8 ± 7.3 years. Among those with DME history, 52% exhibited proliferative DR. DME patients were older, had longer T1D duration, higher prevalence of other microvascular complications, systolic blood pressure and use of lipid-lowering and antihypertensive medications, along with lower estimated glomerular filtration rate ($P < 0.001$). No significant differences were found in HbA1c or CGM parameters according to DME status. Multivariable logistic regressions indicated a trend towards higher DME risk associated with increased glycemic variability, assessed by the coefficient of variation (OR = 1.08, 95%CI 0.99-1.18; $P = 0.068$), and time below range (OR = 1.76, 95%CI 0.92-3.40; $P = 0.090$).
Conclusion
In this cohort of T1D patients, those with history of DME exhibit a worse cardiometabolic profile. We also suggest that higher glycemic variability and time in hypoglycemia may elevate DME risk.

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64

Long COVID is associated with accelerated aging in type 2 diabetes patients

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Background and aims
Leukocyte telomere length (LTL) is considered as a promising prognostic marker associated with COVID-19 severity, adverse outcomes (hospital admission, need

for critical care, respiratory support), and mortality. However, LTL contribution to long COVID development is unclear. In this study, we aimed to evaluate the relationship between LTL and long COVID development in type 2 diabetes patients (T2D) concerning clinical phenotype, gender, and biological age.
Material and Methods
In this cross-sectional study, 68 T2D patients were enrolled. Inclusion criteria: age over 18 years, presence of T2D and COVID-19 infection confirmed by positive RT-PCR test. Patients were divided into 2 groups depending on long COVID presence: long COVID group ($n = 46$) and patients who didn't develop post COVID syndrome (comparison group, $n = 22$) for up to 6 months after COVID-19 infection. A standardized method of quantitative monochrome multiplex polymerase chain reaction in real-time was used to determine the relative LTL.
Results
Our research showed significantly lower LTL in T2D patients with long COVID compared to the comparison group (1.1 ± 0.2 vs 1.28 ± 0.24; $P = 0.003$). LTL negatively correlated with IL-6 ($r = -0.318$; $P = 0.035$) and hs-CRP levels ($r = -0.322$; $P = 0.033$) in the long COVID group, reflecting the role of inflammation in accelerating senescence though there was no statistically significant difference in IL-6 and hs-CR. In sub-analysis shorter LTL was observed in females and patients older in both groups. Shorter LTL was an independent predictor associated with the development of long COVID in patients with T2D (OR 0.026; 95%CI 0.002-0.354; $P = 0.006$). LTL with a cut-off value ≤ 1.02 can be considered as prognostic biomarker of long COVID development (sensitivity 39.1%, specificity 95.5%). The AUROC for the model was 0.691 95% CI 0.561-0.820 ($P = 0.004$).
Conclusions
The results of this study demonstrated that long COVID is associated with an accelerated aging pattern of LTL that could impact the future course of T2D and patients outcomes.

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48

There is a need for better implementation of DKA guidelines - findings from the DEKODE DKA study

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Introduction
In 2021, a new recommendation was put forward by the Joint British Diabetes Society-Inpatient (JBDS-IP) group to reduce fixed rate intravenous insulin infusion (FRIII) from 0.1 to 0.05 units/kg/hour when blood glucose falls <14 mmol/l in the management of Diabetic Ketoacidosis (DKA). This helped reduce the risk of associated complications. However, there has not been any evidence on whether this has been appropriately implemented.
Methods
We performed a retrospective review of DKA admissions between October 2021 and March 2023 across five hospitals in the United Kingdom. We collated data on demographics, biochemical profiles, management interventions, complications, and outcomes.
Results
We identified 753 DKA admissions. The new guidelines were adopted very slowly across hospitals. We saw that there was a significant lag (median[IQR] hours) between starting 10% Dextrose and FRIII rate reduction in DKA episodes where blood glucose became <14 mmol/l (0.5(0.1–1.8) vs 3.2(0.7–6.5), $P = .00001$)). There was no significant reduction in hypoglycaemia (16.5% vs 13.8%, $P = .344$) in episodes that adopted FRIII reduction. There were no significant differences in the frequency of complications and total DKA duration in episodes where FRIII was reduced.
Conclusion
Our study demonstrates suboptimal adoption of guidelines. This could explain why there was no real-world improvement in the incidence of complications and outcomes in DKA episodes where FRIII was reduced. In DKA episodes where FRIII rate reduction was adopted, there was a significant delay in adjusting the FRIII when glucose levels were <14 mmol/l. We must understand the barriers involved in the correct implementation of the new guidelines and identify facilitators, and create appropriate resources. We propose a checklist for 3, 5, 9 & 13 hours into DKA management.

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137

Partial familial lipodistrophy - 2 case reports

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Introduction
Familial partial lipodistrophy (FPL) is a rare genetic disorder characterized by a progressive loss of adipose tissue from various areas of the body. Associated complications include diabetes mellitus, hypertriglyceridemia, non-alcoholic fatty liver disease, polycystic ovaries, acanthosis nigricans, premature atherosclerosis.
Case presentation
The first case is about a 19-years-old woman, known with insulinoresistance (under metformin) and hipothyroidism after thyroidectomy for Graves disease (histopathology: papilary microcarcinoma). The clinical examination revealed a BMI of 22.43 kg/m^2, preserved subcutaneous fat tissue on the facial and cervical regions, with reduced adipose tissue on the upper and lower limbs, thorax and abdomen, cervicalacanthosis nigricans andcafé au lait spots with irregular pattern on the anterior right hemithorax. The laboratory investigations showed an elevated insulin level (72.4 microU/ml), a HOMA index of 17.1 and mixed dyslipidemia (LDLc = 150.8 mg/dl, triglycerides = 221 mg/dl, HDLc = 28 mg/dl). NGS sequencing revealed a pathogenic variant in the IGF1R gene. The second patient is a 35-years-old womanwith a history of poorly managed hypertriglyceridemia. Clinical examination showed a BMI of 24.9 kg/m^2, moderate lipodistrophy on the lower limbs and mild acanthosis nigricans on the cervical region. The laboratory investigations showed severe hypertriglyceridemia (under treatment with omega-3 acids, rosuvastatin, ezetimib), and severe insulinoresistance (insulin = 46.02 mcroU/ml, HOMA index = 12.3). The evaluation also diagnosed a polycysticovary syndrome (suggestive ovarian ecography, clinical and paraclinical hyperandrogenism).
Conclusion
The standard-of-care in lyposidtrophy is to manage the metabolic complications of the disorder, with options including lifestyle modification (diet and exercise) and pharmacotherapy for each specific complication. However, these conventional therapies do not address the underlying causes and often provide insufficient metabolic control, so both patients will receive metreleptin (recombinant analogue of human leptin).

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66

Low mitochondrial DNA is associated with post-COVID-19 syndrome in patients with type 2 diabetes

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Introduction
Post-COVID-19 syndrome (PCS; long COVID-19, post-acute COVID-19, long-term effects of COVID-19) is an emerging health problem in people recovering from COVID-19 infection within the past 3-6 months. The study of COVID-19 severity markers and the assessment of PCS prognosis have encouraged the discovery of the molecular mechanisms responsible for PCS and inevitable pathological conditions. Aim: to define the links between mitochondrial (mt)-DNA levels in blood leukocytes and post COVID-19 syndrome (PCS) development in type 2 diabetes patient (T2D) with regard to clinical phenotype, gender, and biological age.
Methods
in this case-control study, 65 T2D patients were selected. Patients were divided on 2 group depending on PCS presence: PCS group ($n = 44$) and patient who didn't develop PCS ($n = 21$) for up to 6 months after COVID-19 infection. A standardized qPCR method was used to measure the mt-DNA content.
Results
We observed significantly lower mt-DNA content in T2D patients with PCS as compared to those without it (1.26 ± 0.25 vs 1.44 ± 0.24; $P = 0.011$). In gender-specific and age-related analysis mt-DNA amount didn't differ significantly between subgroups. In a comparative assessment depends on PCS clinical

phenotype also a significant difference between mtDNA content not found ($P = 0.572$). In the stepwise multivariate logistic regression analysis, low mtDNA content was independent of oxygen, glucocorticoid therapy and COVID-19 severity associated with the PCS development. The mtDNA with a cut-off value ≤ 1.62 can be considered as a biomarker of PCS development in T2D patients with sensitivity – 93.2% and specificity – 42.9%. The AUROC for the model was 0.687 (95% CI 0.541-0.832; $P = 0.012$).

Conclusions

The low mtDNA content in leukocytes was associated with PCS development in T2D patients, and its decrease could be used as a potential diagnostic biomarker.

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94

Normocytic anemia and its associated factors among type 2 diabetes mellitus

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Introduction

Anemia is one of the important complications of diabetes mellitus (DM), adversely affecting the progression and development of other diabetes-related complications. Despite this, little information is available on the prevalence of anemia and its associated factors in type 2 diabetes mellitus (T2DM). These associated factors are older age, worsening renal function, cardiovascular disease (stroke or ischemic heart disease), peripheral vascular disease, longer duration of T2DM and not using Angiotensin Converting Enzyme(ACE) inhibitor/Angiotensin 2 Receptor Blocker (ARB). Based on this information, our study was designed to investigate the role of factors associated with anemia in T2DM.

Methods

Patients with normocytic anemia (NCA), either unexplained or related to chronic kidney disease, were recruited from our endocrinology clinic over sixty months. We retrospectively reviewed the medical records of 249 patients with NCA whose estimated glomerular filtration rate (eGFR) was greater than 30 ml/min/1.73 m2. Anemia was hemoglobin $<$ 130 g/l for men and $<$120 g/l for women. Relevant data were obtained through a review of medical records.

Results

The prevalence of NCA was 11,7% (29) of the patients. When patients were divided into two groups based on the presence of anemia; age was statistically significantly higher (74 vs. 69 years, $P < 0.001$) and glomerular filtration rate was statistically significantly lower (61 vs. 79 ml/min/1.73 m2, $P < 0.001$) in the group with anemia. However, the duration of T2DM, glycosylated hemoglobin (Hba1c), insulin use, ACE-ARB use, other comorbidities, smoking, and alcohol history were comparable.

Conclusion

Nomocytic anemia in patients with T2DM is associated with older age and lower GFR values. Therefore, screening for anemia should be incorporated into the routine assessment of diabetic complications, particularly for those with significant associated factors.

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13

Diabetic striatopathy in a patient with uncontrolled hyperglycemia: a rare case report

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Introduction

Diabetic striatopathy (DS) is a rare and potentially fatal complication observed in individuals with uncontrolled hyperglycemia. Its prevalence, estimated at less than 1 in 100,000, underrepresents its true incidence, owing to the lack of knowledge about it in physicians. The highest prevalence was seen in Asia (71.6%), Europe (8.5%), and America (4%). Older Asian women were more affected, however, 6 cases were reported in pediatric patients.

Case presentation

A 65-year-old Asian male patient with a history of poorly controlled type 2 diabetes mellitus (DM) and hypertension for 10 years presented with an 8-day history of unilateral, arrhythmic, involuntary, rapid, and non-purposeful choreiform and ballistic movements of the left arm and left leg. The movements were acute in onset, non-progressive in nature, and not associated with any loss of consciousness or orientation, speech disturbances, and convulsions. The random blood sugar level was 536 mg/dl. Laboratory investigations showed glycated hemoglobin (HbA1c) 11.80%.T1-weighted Magnetic resonance imaging (MRI) of the brain showed hyperintensity involving the right posterior putamen. Based on the presence of occurrence of chorea and hemiballismus along with hyperintensity seen in the right putamen on T1-weighted brain MRI and HbA1c of 11.80%, a diagnosis of diabetic striatopathy was made. Sliding-scale subcutaneous insulin glargine was given to achieve glycemic control. Oral tetrabenazine (12.5 mg once a day) and oral clonazepam (0.5 mg once a day) were given to treat chorea and relax skeletal muscles respectively. After 3 days, glycemic control was achieved and chorea subsided. He was discharged with a suitable insulin regimen and 12.5 mg/day oral tetrabenazine.

Conclusion

This case illustrates a rare condition of diabetic striatopathy in a patient with poorly controlled type 2 diabetes mellitus. The presenting features of this condition often mimic a stroke so definitive diagnosis is required with neuroimaging. The mainstay of treatment remains glycemic control, however, anti-chorea drugs may be needed for symptom management.

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62

An animal model for heart failure with preserved ejection fraction (HFpEF)

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Introduction

A strong association exists between obesity and heart failure with preserved ejection fraction (HFpEF). Obesity, usually induced by a high-fructose/high-fat Western diet, is one of the main causes of HFpEF. Here, we compare the cardiac and metabolic effects of different diets in combination with the NO-synthase inhibitor L-NAME (LN) in male Wistar rats.

Methods

Male Wistar rats were randomized into the following groups ($n = 6$, all receiving L-NAME via drinking water): standard diet (standard), a high fructose but low fat diet (LFD) or a high fructose/high fat diet (HFD). An additional group was fed a standard diet without L-NAME (standard without LN). After 16 weeks, blood and heart samples were harvested. Cardiomyocytes as well as mitochondria were isolated. Sarcomere length, cytosolic Ca2+, and mitochondrial redox state, membrane potential and ROS in myocytes were measured using a manual and an automatic Ionoptix fluorescence setup. In isolated mitochondria, mitochondrial respiration, membrane potential, Ca2+-retention capacity and H2O2 production were examined.

Results

A substantial increase in plasma BNP ($P < 0.001$), diastolic dysfunction with preserved fractional shortening, increased diastolic and systolic and Ca2+ transient amplitude was observed only in the HFD group compared to standard without LN. The mitochondrial redox state of HFD group was oxidized, while mitochondrial membrane potential was more stable vs standard and vs LFD in the presence of pyruvate/malate, but not fatty acids. Independent of the given substrate, Ca2+-retention capacity and H2O2 production were not different between groups.

Conclusion

Only the combined treatment of a high fructose/high fat diet and L-NAME is sufficient to generate calcium mishandling and mitochondrial dysfunction typical for HFpEF. Overall, this model promises to be a valid model for examining the effects of HFpEF and, beyond that, the effects of anti-obesity drugs.

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Interdisciplinary Endocrinology

29

Similar recurrence and survival in pre- and post-renal transplant papillary thyroid cancer: data from a 1507 recipient registry

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Introduction
Thyroid nodules discovered during pre-transplant evaluation may delay the transplantation process. While studies suggest an increased incidence of thyroid cancer following solid organ transplantation, the impact on prognosis in papillary thyroid cancer (PTC) among renal transplant recipients remains unclear.
Methods
We conducted a retrospective review of renal transplant recipients with a history of PTC at our institution between 1998 and 2023. Patient demographics, tumor characteristics, treatment details, and outcomes were analyzed.
Results
Among 1507 renal transplant recipients, 11 patients (0.7%) were diagnosed with PTC. Of these, six patients (55%) had PTC prior to transplantation (pre-transplant group), while five patients (45%) developed PTC post- transplantation (post-transplant group). The median age at PTC diagnosis was 51 years (range: 38-59) in the pre- transplant group and 55 years (range: 37-74) in the post-transplant group. In pre-transplant group, the median time from PTC diagnosis to transplantation was 43 months (range 1-166), while three patients had recent (1 to 3 months) thyroidectomy before transplantation. The median time to PTC diagnosis in the post-transplant group was 11 months (range: 5-110). The majority of patients had stage I ATA risk score (pre-transplant: 83%, post-transplant: 75%). Recurrent PTC was not observed in pre-transplant and post-transplant groups with median follow-ups of 57 months (range:14-233) and 143 months (range:32-221) respectively. The survivals of pre-transplant and post-transplant groups did not differ (log-rank test, $P > 0.05$).
Conclusion
In this retrospective analysis, renal transplantation did not significantly impact the prognosis of patients with PTC. Recurrence rates and survival outcomes were comparable between pre-transplant and post-transplant PTC patients. The presence of PTC or thyroid nodules should not preclude patients from undergoing renal transplantation.

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129

Retinal microvascular changes with OCT angiography and serum gremlin-1 levels in acromegaly: a case-control study

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Introduction
Increased GH and IGF-1 levels in acromegaly results in several micro and macrovascular changes. There are controversial results about the effects of GH/IGF-1 on retinal vasculature. Gremlin-1 is a BMP-4 antagonist which binds to VEGFR to activate its pathway and has demonstrated angiogenic properties on several tissues. We aimed to detect retinal changes in acromegaly and examine its association with serum gremlin-1 levels.
Methods
We included 53 acromegaly patients and matched 30 healthy controls. For the evaluation of deep and superficial vascular density and foveal avascular zone (FAZ) OCTA imaging was performed by Optovue (Fremont, CA). Gremlin -1 levels were measured by ELISA method.
Results
Deep ($P > 0.001$) and superficial foveal densities ($P = 0.002$) were significantly lower in acromegaly patients compared to controls. Additionally perifoveal retinal thickness was significantly reduced compared to controls ($P = 0.027$). Plasma gremlin -1 levels were significantly lower in the acromegaly group ($P = 0.015$). No significant difference was detected between active acromegaly ($n = 32$) vs controlled acromegaly ($n = 21$). GH and IGF were negatively correlated with superficial foveal density ($r = -0,242$ $P = 0,046$; $r = 0,-263$ $P = 0,028$) Deep foveal density was negatively correlated with GH and IGF ($r = -0,239$ $P = 0,005$; $r = -0,241$ $P = 0,045$) A negative correlation was detected between Gremlin and FAZ ($r = -0,242$ $P = 0,035$) All participants were evaluated in terms of glucose tolerance status.
Conclusion
Besides the elevations in GH and IGF-1, metabolic alterations like glucose intolerance, hypertension, hyperlipidemia also effects vascular structure and function. In our study, parameters of vascular density were found lower in acromegaly group compared to controls. This indicates a reduction in retinal vessel density. Also it is of note that vascular density is negatively correlated with GH/IGF. In terms of metabolic alterations, vascular density was still significantly lower when the groups were categorized for glucose intolerance. Gremlin, which is considered as an angiogenic molecule, was also lower in acromegaly.

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51

Putting two and two together: a rare case of mccune-albright syndrome

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Introduction
McCune-Albright syndrome (MAS) is a rare genetic disorder caused by somatic gain-of-function mutations in the GNAS gene, leading to persistent activation of the stimulatory alpha subunit of the G protein cellular signaling complex and dysregulated cyclic AMP production in the target tissues. The phenotype, although highly variable, is classically defined as the triad of fibrous dysplasia of the bone, cafe-au-lait skin macules and hyperfunctioning endocrinopathies.
Case presentation
We report the case of a 26-month-old female patient who initially presented with vaginal bleeding and sinus tachycardia, further investigations revealing gonadotropin-independent precocious puberty in association with non-autoimmune hyperthyroidism and prompting the initiation of thiamazole treatment. These findings were followed by a wrist X-ray, which showed an advanced bone age, a pelvic ultrasound and a pelvic MRI, where multiple ovarian cysts were identified. The patient was referred to the department of Paediatric Surgery for intermittent ovarian torsion, where laparoscopic enucleation of the cysts was performed with temporary clinical and biological resolution of the precocious puberty. However, due to the recurrent character of the estrogen-secreting ovarian cysts, treatment with aromatase inhibitor was later initiated. Given the clinical presentation and the hormonal profile together with a personal history of three bone fractures and three cafe-au-lait skin macules, McCune-Albright syndrome was suspected and genetic testing is underway.
Conclusion
Although rare, McCune-Albright syndrome should be considered in case of precocious puberty in association with other hyperfunctioning endocrinopathies. A comprehensive examination along with regular follow-up to assess for clinical improvement and detect the appearance of other manifestations are needed in order to manage this challenging disorder.

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49

Revealing fahr's syndrome in a patient previously misdiagnosed and treated for epilepsy: a case report

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Introduction
Hypoparathyroidism with abnormal calcium deposits in the basal ganglia is known as Fahr's syndrome, a rare condition affecting fewer than 1 in 1,000,000

people, typically those aged 40-60. In contrast, Fahr's disease is characterized by isolated brain calcification without underlying metabolic or endocrine disorders. Both conditions often manifest with neurological and cognitive disorders, seizures, and sometimes psychosis. However, symptoms of Fahr's syndrome usually improve once calcium levels normalize.

Case presentation

We report the case of a 58-year-old male who presented to our emergency department with a generalized tonic-clonic seizure and a prolonged postictal state. Despite intravenous administration of benzodiazepines, there was no improvement. According to his relatives, the patient had a 12-year history of seizures, not well-controlled by anticonvulsive therapy. A head CT scan revealed bilateral symmetrical calcification of the basal ganglia, dentate nuclei, thalamus, corona radiata, and semi-oval calcification of white matter. Laboratory tests showed severe hypocalcemia, significantly low parathyroid hormone levels, mild hypomagnesemia, hypokalemia, and hyperphosphatemia. He had no history of thyroidectomy or parathyroidectomy. Initial creatinine and liver function tests were elevated but soon normalized. ECG was normal. Primary idiopathic hypoparathyroidism was considered and the diagnosis of Fahr's syndrome was made. Considering the possibility of autoimmune polyglandular syndrome, glucose, cortisol, and thyroid-stimulating hormone were checked, and no abnormalities were observed. Immediate treatment included intravenous calcium gluconate, calcitriol, oral calcium, magnesium, and potassium supplements. The patient's disorientation and abnormal movements disappeared as his calcium levels normalized. Over a three-month follow-up, his ongoing treatment for hypoparathyroidism kept his calcium level stable, he remained seizure-free even on minimal anticonvulsant dosing.

Conclusion

Unfortunately, the vague neurological symptoms and low awareness of the link between basal ganglia calcification and hypoparathyroidism often lead to misdiagnosis and ineffective treatment. Sharing knowledge about this condition could help diagnose Fahr's syndrome timely and initiate optimal treatment.

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136

In vitro evaluation of the HEK293 cell line as a model to measure glucocorticoids activity

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Introduction

Glucocorticoids (GCs) are closely related to cortisol and the dysregulation of its secretion can lead to the onset of disorders. Cushing's syndrome (CS) is the clinical manifestation of hypercortisolism and can also develop in subjects who voluntarily or accidentally take high GCs doses. The aim of this study is to conduct preliminary investigations to characterize the HEK293 cell line, to evaluate its response to GCs and to compounds with GC-like activity.

Methods

Cells were incubated for 48H and 72H with different Dexamethasone concentrations ([Dex]) (phase 1: 1-100 mM; and phase 2: 0,25-5 mM) and cell proliferation rate was assessed by cell counting, compared to untreated cells (C). To confirm specificity, incubations with Mifepristone ([Mif]), a GCs antagonist binding GR catalytic site, were also performed. Data analysis was performed using a two-sample independent t-test. A P-value $\leq$ 0,05 was considered significant. Results: The results show that HEK293 cells in phase 1 had significant cell mortality rate (48H: 1 mM (42%), 5 mM (70%), 10 mM (76%), 50 mM (74%), 100 mM (78%); 72H: 5 mM (83%), 10 mM (82%), 50 mM (91%), 100 mM (89%)); in phase 2 cell mortality rate were slightly lower (48H: 1 mM (37%), 2,5 mM (36%), 5 mM (47%); 72H: 0,25 mM (37%), 0,5 mM (56%), 1 mM (49%), 2,5 mM (59%), 5 mM (71%)). The EC50-Dex were: 3,3 mM (48H) and 0,70 mM (72H). Cells were also incubated with increasing ([Mif]) w/o EC50-Dex to test specificity. The minimum [Mif] that blocked the antiproliferative effects of Dex were 50 mM (48H: 52%) and 0,70 mM (72H: 160%).

Conclusion

This cellular model seems to be a valid *in vitro* model for the evaluation of GCs or GCs-like activity. The latter may be present in substances or products that are used daily and therefore difficult to detect.

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132

Complexity and multimorbidity in autoimmune polyendocrine syndrome type 2 – a case report

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Introduction

Autoimmune polyendocrine syndrome type 2 (APS-II) is characterized by the presence of at least two of the following autoimmune disorders: Addison's disease, and autoimmune thyroid disease or diabetes mellitus. It is the most prevalent form of autoimmune polyendocrine syndrome and can be accompanied by other autoimmune disorders, leading to a range of clinical pictures.

Case description

We present the case of a 57-year-old woman with a complex medical history illustrating the diverse clinical manifestations of APS-II. The patient, previously diagnosed with Addison's disease, Hashimoto's thyroiditis, asthma, and coeliac disease, was admitted to the hospital for diagnostic purposes. She presented gastrointestinal symptoms, predominantly loose stools, and bloating, despite strictly adhering to a gluten-free diet. This adherence was proven by laboratory tests, showing normal levels of anti-transglutaminase and anti-gliadin antibodies. During the patient's hospital stay, she underwent a colonoscopy with sample collection. Based on the result of a histopathological examination, lymphocytic colitis was revealed. She was treated with budesonide, resulting in significant clinical improvement. In addition, the patient reported progressively worsening fatigue, particularly after physical activity, and frequent choking with difficulty swallowing over the past three years. Upon neurological examination, she presented mild weakness in facial, neck, and lower limb muscles, as well as diplopia when looking up. Further evaluation confirmed the suspected diagnosis of myasthenia gravis based on significantly elevated levels of anti-acetylcholine receptor antibodies.

Conclusion

The presented case report underscores the complexity of the medical issues associated with autoimmune polyendocrine syndromes. The varied clinical picture and the multitude of accompanying conditions can substantially delay making the correct diagnoses and initiating adequate treatment.

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Pituitary and Neuroendocrinology

110

Growth with something other than growth hormone in children with craniopharyngioma

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Introduction
Despite their benign character, craniopharyngiomas tend to have an unpredictable evolution even after surgical treatment, while the onset of surgery-related growth hormone deficiency is frequently noted. As a part of the multihormonal process that promotes linear growth in GH-deficient children, other mechanisms (like hyperinsulinemia, hyperleptinemia, hyperprolactinemia, hypoestrogenism, low levels of IGF binding protein and possible GH variants) may be involved, aspects included under the concept of "growth without GH".
Case presentation
We present a series of paediatric patients with craniopharyngioma regarding the progression of stature, weight and hormonal parameters. All underwent complete resection of the tumour and then developed GH deficiency (IGF-1 under -2 S.D). We also present the challenges faced during substitution therapy with recombinant GH (rGH). N.I. (14-year-old, female), M.D. (15-year-old, male) and D.D. (6-year-old, male) developed postoperative hyperphagia and hypothalamic obesity. During follow-up was noted a significant increase in stature (N.I currently at +3,03 S.D, M.D. at +2.65 S.D.), likely secondary to adiposity (latest BMI = 38 kg/m^2, respectively 41,07 kg/m^2), insulin resistance and hyperleptinemia. In the case of D.D., he reached +2,68 S.D. for weight, but his stature maintained in evolution a constant position on the growth curve at -1.49 S.D. Patient C.I. (12-year-old, female), initially referred for hypostature (-2,73 S.D), developed obesity after the tumour resection (latest BMI = 29,1 kg/m^2, +2.56 S.D). Her stature progressed up to -0,73 S.D without replacement therapy.
Conclusion
Growth without GH is infrequent, often involving hyperinsulinemia through activation and redistribution of IGF-1. Independent of the alternative pathway involved, we observe that GH deficiency does not prevent linear growth in some children with craniopharyngioma. Substitution therapy during childhood with low dose rhGH is considered to be safe, given the pro-proliferative, angiogenic and anti-apoptotic effects of GH. It also positively impacts quality of life, body composition and fights against low bone mineral density and dyslipidemia.

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35

Cannulated prolactin a forgotten test which can be cost saving

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Introduction
One of the most common referrals to a general endocrine clinic is hyperprolactinemia. It's very difficult to differentiate between stress induced hyperprolactinaemia and true hyperprolactinaemia and may result in unnecessary endocrinology appointments and imaging.
Methods
We have collected data for 60 patients who had a cannulated prolactin test between January 2017 and April 2024 in the Royal United Hospital of Bath (RUH). After cannula insertion, prolactin was measured at 0,30,60 and 90 minutes.
Results
After cannulated prolactin: 30% confirmed high prolactin and 70% confirmed normal results. 42 normal results when did nadir prl occur: 0 min sample: 5%; +30 min sample: 7%; +60 min sample: 7%; +90 min sample: 81%. 18 abnormal results when did nadir prl occur: 0 min sample: 6%; +30 min sample: 22%; +60 min sample: 33%; +90 min sample: 39%. This highlights important to do a full 90 min test given nadir most commonly occurs at 90 mins in both groups, although a bit more spread out in the abnormal test results. 16 patients (26,6%) with abnormal prolactin had MRI performed and 2 patients were still waiting. As a result of this test, we have saved 41 MRIs as just one patient with a normal cannulated prolactin had MRI pituitary and it was normal. His MRI was performed before the cannulated prolactin. Total cost of MRI: £300. Total cost of completing a cannulated prolactin test: £ 76.11. Total cost of 2 outpatients appointments: £372. Therefore, we have saved £ 12,300 and we have saved 2 outpatient appointments per patient which means that we have saved another £ 15,252.
Conclusion
Cannulated prolactin is a very good cost-effective test for diagnosing true hyperprolactinaemia. In summary, we are planning to introduce a new pathway for Hyperprolactinaemia which should include: referral to endocrinology after 2 raised consecutive prolactin in primary care should be made, endocrinology will arrange a 90 min cannulated prolactin test, if still abnormal: arrange MRI pituitary and 2 clinic appointments.

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108

Double trouble: adipsic diabetes insipidus and panhypopituitarism in isolated hypothalamo-pituitary langerhans cell histiocytosis

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Introduction
Langerhans cell histiocytosis (LCH) is a multi-organ disease characterized by clonal proliferation of immature dendritic cells. Isolated hypothalamo-pituitary (HP-LCH) involvement is rare and the coexistence of empty sella syndrome (ESS) is even rarer. We report a case of LCH with ESS and adipsia presenting as life-threatening hypernatremia.
Case presentation
A previously healthy 26-year-old woman presented with amenorrhea, headaches, somnolence, high-grade fever, altered behavior, cognitive decline and inability to recognize relatives. Her relatives noted her loss of thirst sensation. She was delirious and dehydrated with initial investigations revealing hypernatremia (Na-172 mEq/l) with Acute Kidney Injury (Urea-48 mg/dl, Creatinine-1.97 mg/dl), Serum Osmolality 387-mOsm/kg and Urine Osmolality-747 mOsm/kg. Fluid replacement uncovered the co-existing Arginine Vasopressin deficiency (AVP-D). MRI Brain showed T1/T2 iso-intense heterogeneously enhancing irregular suprasellar lesion (2.6 × 1.9 × 2 cm) with loss of interface with hypothalamus, basal ganglia and midbrain, partial empty sella and absent posterior pituitary bright spot. Anterior pituitary workup revealed 8 am cortisol-1.36 mg/dl, TSH-2.312 mIU/l, fT4-0.46 ng/dl, fT3-2.03 pg/ml, Prolactin-0.25 ng/ml, IGF-1-55.42 ng/ml, FSH-0.59 mIU/ml, LH-<0.01 mIU/l. Serum and CSF AFP and HCG were negative. Hormonal treatment was initiated. Whole-body PET-CT showed FDG-avid (SUVmax-25.56) well-defined suprasellar irregular soft tissue density, measuring 1.5 × 2 cm. Stereotactic diagnostic Brain Biopsy was performed. IHC was strongly positive for CD1a, compatible with LCH. 20Gy/10# Radiotherapy (RT) given using VMAT Technique. 6 weeks post RT, her cognition and thirst sensation has returned and 30% radiological improvement was noted.
Conclusion
LCH should be considered in cases of adipsia with AVP-D, even in the absence of other systemic features. Isolated HP-LCH can easily be misdiagnosed; therefore, a biopsy is necessary for an accurate diagnosis to initiate timely and targeted therapy. Adipsia with cognitive impairment led to life-threatening hypernatremia, posing significant management challenges that required ongoing caregiver counseling and support. This case highlights the essential role of a multi-disciplinary approach in navigating the complexities of this disease.

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117

Neurocognitive and neuropsychological assessment in the acromegalic patient: correlation with the clinical, biochemical and prognostic features

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Acromegaly is a rare disease caused by the presence of a sporadic growth hormone (GH)-secreting pituitary/neuroendocrine adenoma. Patients with

acromegaly progressively go through disfigurement of somatic features and relevant systemic manifestations, induced by chronic exposure to growth hormone. In this context of multimorbidity, it is also necessary to assess the cognitive and neuropsychological picture, which is often compromised. In order to perform a comprehensive assessment of cognitive performance and neuropsychological profile in a cohort of acromegalic patients and investigate their correlation with clinical, biochemical and prognostic features, a single-center prospective study was conducted at our Institution in 2023. The population examined consisted of 50 acromegalic patients, 27 women (54%) and 23 men (46%), being treated at the Gemelli Polyclinic Pituitary Outpatient Clinic. All of them were subjected to various neuropsychological questionnaires and tests on reported quality of life. In addition, they were administered neurocognitive tests to the 7 patients in the cohort who were over 65 years old. The most prominent complaints found were fatigue (84%), irritability (82%), emotional changes (76%), work difficulties (70%), increased sensitivity to stress (68%), frustration (62%), physical pain (56%), decreased libido (56%), memory problems (52%) and sadness (50%). The results of the study showed that cognitive and neuropsychological disorders are present to a greater extent in patients with acromegaly than those found in the general population. These alterations were also correlated with independent factors such as age, gender, and the results of the AcroQoL questionnaire, thus allowing the identification of the categories of acromegalic patients at higher risk for neuropsychological disorders. In conclusion, it is essential, in taking care of the patient with acromegaly, to undertake a multidisciplinary diagnostic-therapeutic pathway that is able to take into account the peculiarities of the patient's neurocognitive and neuropsychological profile, with a view to best practice.

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25

Efnb2 controls pituitary development by regulating the pituitary stem cell niche

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Efnb2 plays an integral role during mouse development and in the adult stem cell niche. Efnb2 does encode for Ephrinb2 ligand which then binds to Eph receptor. Preliminary data suggest implication of Efnb2 in pituitary tumours and during normal pituitary embryogenesis. Currently, involvement of Eph:Ephrin signalling pathway in pituitary development is unknown. Better knowledge of Efnb2 in the pituitary will help to improve understanding of endocrine diseases. Deletion of Efnb2 in early pituitary progenitors was performed *in vivo* using the pituitary specific Hesx1 Cre-driver. Efnb2 is expressed in the pituitary from early development in stem cells; hence, it suggests a role in the maintenance of pituitary stem cells (PSCs). Conditional pituitary knockout mice exhibit severe hyperplasia and morphological abnormalities within the gland. To further understand molecular mechanism by which Efnb2 controls the pituitary, mRNA sequencing was done during early embryonic stages of pituitary development. Transcriptomic analyses include cell populations of Efnb2+/+ as well as Efnb2-/-. RNA sequencing reveals novel functions of Efnb2 in proliferation, epithelial integrity, and cell lineage commitment. Functional assays were then performed in order to validate these transcriptomic data. First, Efnb2 mutant mice exhibit increased mitotic index both *in vivo* and *in vitro*. Therefore, Efnb2 impacts cell proliferation of PSCs. Secondly, Efnb2 mutants present downregulation of epithelial integrity genes, which does result in abnormal epithelial mesenchymal transition (EMT). Importantly, Efnb2 regulates cell commitment. These events delay commitment as there is a significant reduction of Pomc1, Pit1 and Gsu, known pituitary cell lineage markers. In conclusion, Efnb2 is critical for pituitary development as it regulates the niche of PSCs. Our results demonstrate a novel role of Efnb2 in pituitary development by regulating cell proliferation, epithelial integrity, and cell lineage commitment of PSCs.

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135

Unforeseen depths of short stature: a case study

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Introduction
Mitochondrial encephalopathy, lactic acidosis and stroke like episodes (MELAS) is one of the most studied and described mitochondrial disorder. However, the markedly variable presentation, particularly among paediatric patients makes diagnosis challenging. Here, we report an unusual manifestation of MELAS in a patient evaluated for short stature with growth hormone deficiency.
Case presentation
A 15 years old female, born out of non- consanguineous marriage, presented with poor height gain since the age of 10 years and absent secondary sexual characteristics with hearing difficulty. Anthropological assessment revealed a height of 133 cm (-3.86 SDS) and weight of 22.2 kg (-4.12 SDS), with proportionate short stature and no eunuchoidism (arm span 135 cm). Bone age was 11 years. Physical examination showed dry, flaky hairs, triangular facies, high-arched palate, and hypertrichosis with Tanner stage 1 for pubertal development. Laboratory findings demonstrated anaemia of chronic disease, elevated lactate (7.8 mmol/l), and low IGF-1 (61.97 ng/ml). She was euthyroid, eucortisolemic with basal LH and FSH levels of 1.74 and 1.33 m IU/l respectively. Growth hormone stimulation test with clonidine was non-stimulated (Peak value-3.73 ng/ml). MRI brain revealed bilateral basal ganglia calcification and cerebellar atrophy. Whole mitochondrial genome sequencing identified a mutation in MT-LT1 gene (n.14A>G variant), confirming MELAS syndrome. Retrospectively, patient had no history of stroke and encephalopathy and no complaints of muscle weakness. Patient was started on growth hormone therapy with CoQ-10 for its neuroprotective effects with plan to observe pubertal progression after correction of underlying conditions.
Conclusion
The presented case exemplifies the diverse and often subtle manifestations of MELAS syndrome. Despite absence of overt stroke-like episodes or muscle weakness at the time of evaluation, the early recognition of MELAS based on these atypical features underscores the importance of considering mitochondrial disorders in cases of unexplained growth failure, endocrine dysfunction, and subtle neurological symptoms.

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104

Pituitary microadenoma in children – diagnostic challenges and traps

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Multiple pituitary hormone deficiency (MPHD) associates variable misleading hypothalamic-pituitary imaging (MRI) aspects, with unpredictable dynamics until puberty, which requires a differential diagnosis with acquired pituitary changes that can modify subsequent case management. The patient, aged 7 years and 4 months, with no significant personal or hereditary antecedents, presented at the age of 5 years and 7 months to the Iasi Endocrinology Clinic for severe short stature (-4.89DS compared to the average height for the age and sex). Through a biological panel, pediatric and genetic consultation, alternative causes of short stature were excluded and endocrinologically, MPHD is confirmed along the thyrotropic and somatotropic axes. The radiograph of the fist illustrates the delayed bone age with 4 years compared to the chronological age and the hypothalamic-pituitary MRI describes the asymmetric pituitary gland with a right paramedian nodular area of 5/5/5 mm that appears in isosignal T1, hyposignal T2, with contrast asymmetry in the sequences made in dynamics, with a small late peripheral uptake of contrast, suggestive of pituitary microadenoma; pituitary stalk not deviated. The PROP1 mutation is the most common cause of congenital pituitary hormone deficiency, whose clinical, biological and imaging presentation pattern aligns with that of the discussed patient up to now. Thus, a neurosurgical consultation is performed; it establishes the interpretation of the imaging aspect in the context of intense regional contrast, through the development of the intercavernous sinuses. Tumor markers AFP, LDH and bHCG (within normal limits) exclude the tumor origin of the pituitary formation, elements that allow hGH substitution, the patient presenting a favorable clinical and biological evolution after 18 months of treatment. The particularity of the case consists in the differential diagnosis of the pituitary imaging aspect in pediatric cases for the establishment of therapeutic and follow-up conduct.

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Reproductive Endocrinology

88

Induction of spermatogenesis in men with hypogonadotropic hypogonadism

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Introduction
Hypogonadotropic hypogonadism (HH) is a type of secondary hypogonadism. Congenital forms are distinguished, including Kallman's syndrome and Idiopathic hypogonadotropic hypogonadism (IHH), along with acquired forms. The incidence of HH in men is 1:10,000.
Case report
A 34-year-old male patient was hospitalized at our department in August 2023 due to primary infertility and sexual dysfunction (SD). The patient was referred to our clinic with results that showed azoospermia and a low testosterone (T) level of 1.72 nmol/l. During physical examination, a small volume of the testis (5 ml) and a spermatocele were found on the left (12 m). Additional stimulation tests (LHRH test and hCG test) were performed during hospitalization and indicated a good testosterone response. The karyotype analysis revealed no abnormalities. All required analyses and findings, including normo-osmium testing, indicated an idiopathic form of hypogonadotropic hypogonadism with consequent infertility and SD. Considering the adequate response in the stimulation tests, the induction of spermatogenesis was initiated with human chorionic gonadotropins (hCG), and Tadalafil was introduced for SD management. One month after the initiation of treatment, check-up findings were favorable (T 24.2 nmol/l). Anastrozole, an aromatase inhibitor, was then added to the treatment regimen. When the T level reached 20 nmol/l, Gonal-f (follitropin alfa) was introduced, resulting in an excellent response to treatment. Five months after treatment initiation, hormonal findings were satisfactory, and semen analysis showed significant improvement.
Conclusion
Timely replacement therapy with gonadotropin analogues in HH men with azoospermia and infertility is effective for stimulating spermatogenesis, improving fertility outcomes, fostering the development of secondary sexual characteristics, and enhancing sexual function.

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23

Previous illicit androgen users display persistently impaired Leydig cell capacity but recovered luteinising hormone secretion

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Background
A general finding among previous illicit androgen male users is persistently lower serum testosterone than nonusers and may be caused by reduced pituitary luteinising hormone (LH) secretion. However, the functional capacity of the testes and pituitary remains to be assessed after androgen use. We compared pituitary-testis-axis capacity in previous illicit androgen users and nonusers.
Methods
We conducted a cross-sectional study including men involved in recreational strength training with and without a history of androgen use. We performed gonadotropin-releasing hormone (GnRH) and human chorionic gonadotropin (hCG) stimulation tests to assess pituitary function and testicular Leydig cell capacity. Serum total testosterone and insulin-like Factor 3 (INSL3) were measured using LC-MS/MS. Sexual function was evaluated by the IIEF-15 questionnaire.
Results
We compared 30 previous users with elapsed duration since androgen cessation, geometric mean (95% CI), 2.0 (1.2;3.5) years and 30 nonusers. Mean (SD) age of all participants was 38 (8) years. The mean (95%CI) increase in testosterone following hCG injection was lower among previous users than nonusers; group difference: -9·4 (95% CI) (-13·6;-5·2) nmol/l, $P < 0{\cdot}001$. We found no differences in LH secretion between groups. In linear regression models using erectile function as dependent variable, higher Leydig cell capacity, expressed as either a serum testosterone increase during the hCG test ($P = 0{\cdot}043$) or INSL3 ($P = 0{\cdot}008$), was independently associated with better erectile function, whereas baseline serum testosterone was not ($P = 0{\cdot}861$).
Conclusion
Previous illicit androgen users presented a persistently decreased Leydig cell capacity but normal pituitary function two years after androgen cessation

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50

Variations in the assessment and education of polycystic ovary syndrome (PCOS) during initial consultations across europe and india: a multinational study

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Introduction
Women with polycystic ovary syndrome (PCOS) are often dissatisfied with the assessment and management of the condition. We aimed to understand the variations in the assessment and education of PCOS during initial consultations.
Methods
This retrospective multinational study was conducted across Europe and India. All women aged above 18 who had their initial consultation in PCOS clinics between 2020 and 2023 were included. Those without PCOS or who were undergoing follow-up were excluded. Data were collected on participants' health and sociodemographic status, reasons for PCOS clinic referral, and parameters assessed during consultation. Data were further analysed according to the year of consultation. Descriptive statistics were performed using SPSS v28.0.
Results
A total of 917 participants were included in this study. 55% ($n = 505$) were from the UK, 26% ($n = 241$) were from Turkey, and 10% ($n = 92$) were from Greece. 629 (68.6%) participants were White. The commonest reasons for referral were irregular menses (62.9%), excess hair growth (56.2%), and acne (31.6%). Irregular menses was the most common reason for referral across all ethnic groups and countries except India, where infertility accounted for most referrals. Participants frequently reported comorbidities, including anxiety (9.2%), hypothyroidism (9.1%), and depression (7.1%). Anxiety was the most common comorbidity in the UK and Georgia and among White and Black/mixed/other ethnic groups. Interestingly, participants from India reported no comorbidity. During consultations, the most assessed parameters were dermatological concerns (89.6%), cardiometabolic (80.0%), and lifestyle management (79.9%). Dermatological concerns were most assessed across ethnicities. Long-term risk management was among the least assessed parameters across ethnic groups. There have been improvements in assessing emotional well-being in recent years, although it was particularly poorly assessed in Black/mixed/other ethnic individuals.
Conclusion
This study highlights the need to assess emotional well-being and long-term risk management during consultations to ensure consistent care across ethnic groups.

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28

Testosterone serum levels predict the severity of metabolic dysfunction-associated steatotic liver disease (MASLD) in hypogonadal men

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Introduction
Metabolic dysfunction-associated steatotic liver disease (MASLD) is defined by the presence of hepatic steatosis and metabolic risk factors. Both testosterone and estradiol play pivotal roles in hepatic lipid homeostasis, though the underlying mechanisms remain unclear. Low serum testosterone levels are independently associated with MASLD. However, no studies have previously evaluated the prevalence and severity of MASLD in hypogonadal men.
Methods
A prospective, observational, clinical trial was conducted enrolling hypogonadal men. Each patient underwent hepatic ultrasound to evaluate the presence and grade of steatosis, and Fibroscan® and 2-dimensional shear weave elastography (2D-SWE) techniques for the assessment of liver stiffness.
Results
Forty-one hypogonadal men (age 57.7 $\pm$ 14.0 years, body mass index 31.9 $\pm$ 6.5 kg/m^2) were enrolled, of which twenty-three (56.1%) were already under androgen replacement therapy. Hepatic steatosis was detected in 30 patients (75.0%), divided into mild (10.0%), moderate (32.5%) and severe (32.5%) grades. No difference in liver steatosis presence/grade was detected between androgen-replaced patients compared to untreated ones ($P = 0.293$). Liver fibrosis was detected in six men (14.6%) at Fibroscan® and in 4 (9.8%) at 2D-SWE. The presence of fibrosis was similar between naïve and treated patients ($P = 0.565$). The presence of liver fibrosis was neither associated, nor predicted by any hormones and biochemical parameter. This lack of significant correlations remained also after subdivision in naïve hypogonadal men and patients under androgen replacement therapy.
Conclusion
Here, we demonstrated a high prevalence of liver steatosis in hypogonadal men, particularly of moderate to severe grades. Moreover, we identified an unexpectedly high prevalence of liver fibrosis, occurring in about 15% of cases. Although our results need further confirmation in larger cohorts, the relatively high prevalence of liver fibrosis in this patient cohort suggests that liver health should be evaluated in the management of male hypogonadism.

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75

Tamoxifen use in gynecomastia: a tertiary centre experience

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Introduction
Gynecomastia is defined as the benign proliferation of breast tissue in men. Although common, only a small portion of patients seek treatment, either for cosmetic reasons, pain, or tenderness. Tamoxifen has been proposed as an alternative to surgical treatment.
Methods
We conducted a retrospective study including all patients referred to our Endocrinology Department between January 2020 and April 2024 due to gynecomastia. Secondary causes were evaluated in every individual, including a thorough hormonal work-up. Patients with pain and/or tenderness, without identifiable reversible causes or contraindications, were selected and treated with tamoxifen 20 mg daily for a three-month period. Response to treatment was subsequently assessed clinically.
Results
A total of 41 patients with a median age of 52 years (range: 21-85) and a median duration of symptoms of 14 months (range: 4-53) were included. Bilateral breast enlargement was present in 25 patients (61.0%). Increased tenderness was reported by 26 patients (62.4%), and significant pain by 16 patients (39.0%). A secondary cause was identified in 18 cases (43.9%), with iatrogenic causes, primarily androgenic steroid use, being the most frequent. Fifteen patients (36.6%) were selected for treatment with tamoxifen. The median symptom duration in this group was 36 months (range: 3-48), and no secondary cause was identifiable in 53.3% of these patients. Thirteen patients reported resolution of tenderness, and eight noticed a decrease in breast size post-treatment. No side effects or relapses were observed. Patients not eligible for tamoxifen were referred to Plastic Surgery.
Conclusion
Gynecomastia has a significant psychological impact in patients' lives and frequently causes pain and discomfort. Tamoxifen seems to be a safe and somewhat effective option and should be considered prior to surgery.

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71

Copy number variations in self-limited delayed puberty

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SLDP is where the onset of puberty is more than 2-2.5 standard deviations later than the population mean age and is often familial with strong genetic determinants. The reproductive axis is regulated by gonadotropin-releasing hormone (GnRH), which plays a crucial role in initiating puberty and maintaining fertility through its pulsatile secretion. Disruption in GnRH neuron development or hypothalamic function can lead to DP. UK Biobank data has identified negative health outcomes associated with SLDP including early menopause/andropause and cognitive and psychosocial disabilities. Consequently, there has been extensive research to investigate genes affecting the hypothalamic-pituitary-gonadal (HPG) axis that might be implicated in the pathogenesis of DP by our group and others which has identified sequence variation contributing to the aetiology of SLDP. However, factors beyond nucleotide variations, such as epigenetic changes and CNVs can also lead to pubertal timing disorders. Moreover, CNVs are seen in multiple individuals ($n = 92$) from the Deciphering Developmental Disorders study (https://www.deciphergenomics.org) with a phenotype including DP (HP:0000823). We performed whole genome sequencing on 49 probands with SLDP and subsequently, analysed the data for CNV. The data was initially called, annotated, filtered then partitioned for classification of CNVs using a command-line tool that implements the ACMG guidelines to evaluate the pathogenicity of germline duplications and deletions. Using an unbiased candidate gene approach, we identified several deletions that affected 60 known/predicted dosage sensitive genes and combines with functional enrichment analysis; This approach revealed potential molecular pathways and biological processes involved in the pathogenesis of SLDP, including neural plate and embryo developments. To refine our findings, we applied additional filters, including known HPG axis genes, GWAS loci associated with pubertal timing, DP gene panels and GnRH neurons RNA sequencing data, to narrow down large number of rare predicted damaging CNVs and prioritize those with potential relevance to DP.

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100

Short-term changes in bone metabolism among transgender men starting gender affirming hormone therapy: a systematic review and meta-analysis

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Introduction
Transgender and gender diverse (TGD) people experience a gender identity which is different from the sex assigned at birth. Some transgender men (TM) can

ask for testosterone to induce virilization and its effects on bone health are still to be fully elucidated. The aim of this systematic review and meta-analysis was to evaluate the changes on bone metabolism in a short-term period among TM starting testosterone.
Methods
A systematic search was conducted in PubMed, Scopus, Web of Science, and Cochrane Library. The articles of interest had to report longitudinal evaluation before starting testosterone and after 12 and 24 months of testosterone among TM. The analyzed parameters were BMD, calcium, phosphate, 25OHD, PTH, P1NP, BAP, osteocalcin and CTx. Mean differences with 95% coefficient intervals were combined using random effects models. Funnel plot, Egger's test, and trim-and-fill analysis were used to assess publication bias.
Results
Fourteen studies met the inclusion criteria, including 1484 TM. In absence of heterogeneity, BMD did not significantly change at lumbar spine, hip, femoral neck, and whole-body evaluations. Calcium, phosphate, 25OHD and PTH remained stable over time. Regarding bone markers, only P1NP showed a statistically significant increase after 12 months of T therapy, in absence of heterogeneity (SMD 0.61 mg/l; 95% CI: 0.40-0.83; $P < 0.0001$; $I2 = 0\%$, Pforheterogeneity = 0.48).
Conclusion
Testosterone therapy among TM seems not to disrupt bone health after 12 and 24 months. A statistically significant increase in P1NP after 12 months of therapy may indicate a positive anabolic effect of testosterone in the short term.

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40

Tyrosine kinase inhibitors: systematic review of their effects on male gonadal function

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Introduction
Tumors in adolescents and young adults are on the rise, and the number of young cancer patients undergoing chronic treatment with targeted therapy is growing. Although much is known about the toxicity of conventional anti-cancer therapies, evidence on tyrosine kinase inhibitor (TKI) effects on fertility is still lacking. This systematic review was undertaken to evaluate the effects of TKIs on male gonadal function to provide adequate counseling to patients undergoing these therapies.
Methods
A comprehensive search of PubMed and Scopus databases was conducted, focusing on the effects of TKIs on spermatogenesis and testicular endocrine function. We included animal studies, observational studies, and case reports published up to December 31, 2023. The identified articles were reviewed and analyzed to evaluate the impact of TKIs on the male gonad, their long-term effects, the reversibility of the observed changes, and the underlying molecular mechanisms involved.
Results
Imatinib, gefitinib, sorafenib, sunitinib, quizartinib, dasatinib, and nilotinib appear to damage spermatogenesis, decreasing sperm count and motility. Mechanisms involved include interference with the KIT system, PI3K, and ERK kinase, affecting spermatogonia maturation and survival. Furthermore, TKIs alter the function of the hypothalamic-pituitary-testicular axis, decreasing serum gonadotropins and testosterone levels. Finally, TKIs appear to have a direct impact on testicular tissue, compromising testicular function and therefore spermatogenesis. However, the extent and severity of these effects may vary between patients and within this class of drugs.
Conclusion
TKIs appear to damage spermatogenesis. Understanding the molecular mechanisms of TKI effects on male reproductive health is essential to providing adequate fertility counseling and managing hormonal imbalances. The paucity of available studies on this topic indicates the need for further research. However, based on these results, we suggest that healthcare providers should discuss the potential impact of this type of treatment on testicular hormone production and fertility and consider sperm cryopreservation to optimize the quality of life of patients recovering from cancer.

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54

Is menopause the answer for a 47 year old woman?

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Introduction
Functional hypothalamic amenorrhea is one of the most common causes of secondary amenorrhea (20–35%) and 3% of primary amenorrhea. FHA can be weight loss-related, stress-related and exercise-related. It results from abnormal GnRH secretion, leading to impairment of gonadotropins and hypoestrogenism.
Case presentation
A 47 year-old female presents for an endocrine evaluation regarding hormone function after 2 years of amenorrhea. She also reported a 40 kg weight loss with dietary management, between 2019-2021, with the cessation of menses after this. Clinical examination revealed a normal BMI, low blood pressure (90/60 mmHg), normal heart rate. Endocrine evaluation revealed a normal palpable thyroid, adipose tissue distribution and senologic exam, no hirsutism or acnee. Biochemistry revealed only a mild anemia with low erythrocyte indices. Hormone evaluation revealed low gonadotropins and estrogen and normal prolactin and total testosterone (panel also tested 18 months ago). Thyroid function was normal. Thyroid ultrasound revealed omogeneous structure, normal vascularisation. Transvaginal ultrasound showed an homogeneous uterus, thin endometrium, micropolycystic right ovary, left ovary unvisualized. A pituitary MRI showed a ~2.1/1.8 mm round-oval image in the right pituitary lobe – possible pituitary microadenoma. We also evaluated other pituitary hormone lines, with no abnormal findings. The patient was started a nutritional, psychological and modified exercise intervention. If these are not suffice, hormone substitution with transdermal estradiol therapy and cyclic oral progestin is considered.
Particularities
The patient's age suggestive for menopause stage. The presence of the non-functional pituitary microadenoma. The 2 year latency between the onset of symptoms and the correct diagnosis.
Conclusion
Because of the delay in the diagnosis, hypoestrogenism may already have had an impact regarding loss of bone mass density, cardiovascular complications, depression and sexual impairment. Regardless of the patient's age, diagnosis and proper management is required to prevent both short- and long-term medical complications.

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68

Anogenital distance in klinefelter syndrome: a case-control study

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Background
Serum testosterone (T) levels may fall at different stages of sexual development in Klinefelter syndrome (KS), whereas overt hypogonadism typically arises after puberty. Nevertheless, normal mini-puberty and puberty are still debated in KS subjects. Anogenital distance (AGD) is an anthropometric parameter under the influence of early life and childhood androgen exposure. Genital anomalies, testicular cancer and oligospermia have been associated with a shorter AGD in men. While other androgen-dependent anthropometric measures such as stretched penis length (SPL) and testicular volume (TV) have been described in KS populations, in this study we focused on AGD, which has never been investigated before.
Objectives
To explore the role of AGD as an anthropometric marker of androgenization in adult KS.
Methods
We evaluated TV, AGD and SPL in 53 KS patients and 101 Caucasian men with normal T levels (> 12 nmol/l), using an orchidometer for TV, a digital caliper for

AGD and a standard meter for SPL. In both groups, AGD was related to hormone levels (T, LH, FSH) and anthropometric characteristics. Results: KS exhibited significantly lower T levels vs controls (9,4 $\pm$ 4,5 nmol/l vs 19,6 $\pm$ 5,1 nmol/l) and markedly lower TV (2,5 $\pm$ 1,1 ml vs 15,4 $\pm$ 4,7 ml), reflecting KS-related hypogonadism. KS and controls had comparable AGD ($P = 0{,}954$), with average values, respectively, of 6,9$\pm$1,6 cm [95% CI 6,4-7,3] and 6,87$\pm$1,44 cm [95% CI 6,6-7,2]. In neither group AGD was correlated to T levels, TV, SPL or arm span. Notably, AGD showed a significant correlation with waist circumference [$P = 0{,}004$] and body mass index [$P < 0{,}001$] only in KS, but not in control subjects. Conclusions: despite lower T levels, KS subjects have similar AGD compared to healthy control and our result support the hypothesis that KS may receive sufficient androgen exposure during mini-puberty and puberty.

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Thyroid

123

Evaluating predictive models for radioiodine therapy success in differentiated thyroid cancer patients

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Introduction
Differentiated thyroid cancer (DTC) is the most common endocrine malignancy, with a notable increase in incidence over recent decades. Despite the generally positive prognosis, managing DTC remains intricate, often involving thyroidectomy followed by radioactive iodine (RAI) therapy. The response to RAI varies significantly among patients, underscoring the need for reliable predictors of treatment efficacy. New guidelines emphasize the importance of personalized follow-up plans, fueling research into predictive models to enhance prognostic precision.
Methods
This retrospective study analyzed 744 DTC patients treated at a single center, focusing on the predictive value of clinicopathological factors and thyroid biomarkers. We developed multivariate logistic regression models to evaluate the efficacy of different biomarkers in predicting RAI response, adjusting for variables such as age, sex, and disease stage. Optimal cut-off values for these biomarkers were determined to assess their predictive capability.
Results
Our analysis found that no single biomarker outperformed others significantly in predicting RAI treatment outcomes. However, stimulated thyroglobulin (sTg) emerged as a reliable predictor, with a mean cut-off value of 7.22 ng/ml. The presence of chronic lymphocytic thyroiditis (CLT) also appeared to enhance the accuracy of the predictive models, though the improvement was not statistically significant.
Conclusions
This study underscores the potential of sTg as a key predictor for RAI efficacy in DTC patients, with a defined cut-off value that can aid in clinical decision-making. Incorporating CLT status into predictive models may further improve their accuracy, suggesting a direction for future research. These findings contribute to the advancement of personalized treatment approaches for DTC patients undergoing RAI therapy, ultimately aiming to improve patient outcomes by tailoring management strategies to individual patient profiles.

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58

Alterations in gut microbiome in patients with autoimmune thyroiditis with hypothyroidism and irritable bowel syndrome with constipation

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Introduction
Autoimmune thyroiditis (AIT) is one of the most common endocrine disorders worldwide met in young patients, which leads to hypothyroidism because of durable autoimmune inflammation. Irritable bowel syndrome (IBS) is a widespread disorder that severely influences the quality of life, and is also prevalent in young patients. The scientific interest is in studying the peculiarities of gut microbiome alterations in patients with the current comorbid pathology.
Methods
The prospective study included 98 patients with AIT and compensated hypothyroidism (AIT-H) with comorbid IBS with constipation (IBS-C): both male ($n = 38$) and female ($n = 60$). The average age of male patients was 41.2 y. o, and 36.7 for female patients. The patients received Levothyroxine 25-150 mg for hypothyroidism compensation. The ultrasound, anti-TPO, and Anti-hTg blood tests were used to diagnose AIT, while the compensation stage was determined by the level of TSH = 1.0-2.5 mIU/l. In patients with IBS-C (diagnosed due to Rome IV criteria), the result of fecal calprotectin test <50 mg/g was used to exclude bowel inflammation. All patients were provided real-time PCR microbiome tests for total bacterial count (TBC), Firmicutes/Bacteroides ratio, E. coli, Fecalibactrerium prausnitzii, Lactobacillus spp., Enterococcus spp., Bacteroides fragilis group/Fecalibactrerium prausnitzii ratio, Bifidobacterium spp., Fusobacterium nucleatum, Roseburia inulinivorans.
Results
In studied patients the bacterial quantity (M ± m) was the following: TBC = 9,31 ± 0,31, Bacteroides fragilis group/Fecalibactrerium prausnitzii ratio 794,57 ± 85,54. Firmicutes/Bacteroidesratio 1,02 ± 0,06, E. coli 6,02 ± 0,32, Bifidobacterium spp. 7,32 ± 0,29, Fecalibactrerium prausnitzii 8,14 ± 0,54, Lactobacillus spp. 5,73 ± 0,31, Enterococcus spp. 6,4 ± 0,5, Fusobacterium nucleatum 3,0 ± 0,1, Roseburia inulinivorans 7,46 ± 0,71.
Conclusion
In patients with AIT-H and IBS-C the amounts of Roseburia inulinivorans and Fusobacterium nucleatum were higher than normal values, while Lactobacillus spp., Bifidobacterium spp., E. coli were lower, and the Bacteroides fragilis group/Fecalibactrerium prausnitzii ratio exceeded the normal. Knowing the gut microbiome alterations can open new management approaches and improve the quality of life of young patients.

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18

Unveiling the mystery of a thyroid nodule: a case report

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Introduction
The thyroid gland, shaped like a butterfly with two lobes connected by the isthmus, is a common site for nodule formation. Only 2-9% thyroid cancers occur in the isthmus. Cancers in the isthmus are more prone to spread beyond the thyroid, leading to a less favourable prognosis. While ultrasound features like a taller-than-wide shape and microcalcifications suggest malignancy in lobar nodules, suspicious characteristics in isthmus nodules are underreported.
Case presentation
A 54-year-old male non-smoker with bronchial asthma, presented with persistent hoarseness of voice for 2 months, facial puffiness, and giddiness. He denied throat pain, fever, cough, dysphagia, or dyspnoea. On examination no palpable neck nodule, lymphadenopathy, or oral cavity abnormalities. CECT of the neck and thorax identified a hypo-enhancing thyroid nodule in isthmus measuring 12 mm × 8 mm. USG confirmed a well-defined isoechoic nodule with a small central cystic component in the left isthmus, classified as TIRADS 3, without calcifications or internal vascularity. Fibre optic laryngoscopy showed mild sluggish movement of the left true vocal cord (TVC) and a small vocal cord nodule on the right side. Fine-needle aspiration cytology (FNAC) was suspicious for papillary thyroid carcinoma (Bethesda V). Thyroid function tests showed a TSH level of 3.34 with normal FT4 and negative anti-TPO antibodies.
Conclusion
Recent studies indicate that thyroid carcinomas in the isthmus have a worse prognosis than those in other locations, with higher rates of lymph node metastases and extrathyroidal extension. This may be due to the isthmus's smaller size, thinner structure, and unique lymphatic drainage. These findings, along with the observation that malignant nodules in the isthmus tend to be smaller, suggest the need for revised American College of Radiology TI-RADS algorithms and new biopsy cutoff values for nodules in this region. This case highlights the importance of thorough evaluation and management of thyroid nodules in the isthmus due to their unique characteristics and prognostic implications.

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146

Challenging reference values for basal and stimulated calcitonin in medullary thyroid cancer diagnosis: a 2 center experience from real life setting

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Introduction
Measurement of basal (bCT) and stimulated calcitonin (sCT) after calcium gluconate infusion can help detect early-stage medullary thyroid cancer (MTC). However there are no standardized cutoffs to discriminate between MTC and other thyroid conditions including c-cell hyperplasia.
Methods
A retrospective analysis was conducted on 62 consecutive calcium gluconate stimulation tests performed in 2 Italian institutions from 2015 to 2024. Patients with known RET mutations were excluded. Basal and stimulated calcitonin were measured with LIAISON-Calcitonin-IIGen assay (DIASORIN). Patients were retrospectively categorized according to commonly used, nationally validated cutoffs: bCT >30 pg/ml and sCT >79 pg/ml for females, bCT >34 pg/ml and sCT >466 pg/ml for males.
Results
Of the 62 patients enrolled, 67% females (22/33) and 24% males (7/29) underwent thyroidectomy. Mean bCT and sCT levels were 48.1 pg/ml and 765.6 pg/ml in MTC, compared to 15.6 pg/ml, 282.9 pg/ml in non-MTC patients. Concordant positive bCT and sCT predicted MTC in 80% of cases. Increased sCT alone resulted in 84% false positives (16/19), predominantly in females. One MTC patient was missed by both bCT and sCT cutoffs. In women, bCT >30 pg/ml had 67% sensitivity and 100% specificity for MTC detection. sCT >79 pg/ml had 100% sensitivity but only 6% specificity. In our series an alternative cutoff of sCT >257 pg/ml could provide 100% sensitivity and 81% specificity. Surgical complications included permanent hypoparathyroidism (41%) and dysphonia (7%). Prophylactic central neck dissection was performed in 66% of cases, leading to higher rates of permanent hypoparathyroidism (53% vs 10%).
Conclusion
Routine calcitonin measurement and calcium gluconate testing can identify preclinical MTC, but carry significant risks of false positives, leading to unnecessary surgery, with relevant morbidity. Given the discordance of literature data, calcium gluconate testing should rely on institution-specific cutoffs. If unavailable, it should be delayed favoring trend monitoring for low bCT values.

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36

Metastasis of clear cell renal cell carcinoma to the thyroid gland resembling papillary thyroid cancer: a case report

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Introduction
Metastatic disease to the thyroid is common due to its rich blood supply, with autopsy series showing prevalence from 1.25% to 24%. The most frequent primary sites include the kidney, lung, breast, head and neck, gastrointestinal tract, and skin. However, non-thyroid malignant tumors are rarely diagnosed clinically and often misinterpreted as primary thyroid tumors, especially in patients with multinodular goiter.
Case presentation
This case involves a patient diagnosed with Clear Cell Renal Cell Carcinoma (ccRCC) of the left kidney at age 40, treated with unilateral nephrectomy and left adrenalectomy. The tumor was graded G1, T2N0Mx. Ten months later, a PET CT scan revealed shoulder blade metastasis, leading to palliative radiation therapy and zoledronic acid administration. A year later, a CT scan identified a mass in the right adrenal gland, confirmed as ccRCC metastasis after right adrenalectomy. Following this procedure, the patient began hormone replacement therapy with mineralocorticoid and glucocorticoid. After ten years (in 2022), a thyroid gland ultrasound revealed a multinodular nontoxic goiter and an 18/15 mm hypoechogenic nodule with microcalcifications in the left lobe of the thyroid gland. A fine needle aspiration (FNA) biopsy was conducted. Cytology was suspicious for either metastasis of ccRCC or papillary thyroid cancer. A total thyroidectomy was performed. Morphology could not differentiate between primary and secondary malignancy, but immunohistochemical staining confirmed ccRCC metastasis. Since then, the patient takes hormone replacement therapy with levothyroxine, without needing thyroid stimulating hormone suppression or thyroglobulin level monitoring.
Conclusion
This case report highlights the importance of careful investigation when identifying nodular goiter in patients with malignancy. Differentiating metastases from primary thyroid cancers is crucial for improving treatment strategies and overall outcomes.

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144

Ultrasound guided percutaneous ethanol injection (PEI) for the treatment of cystic and predominantly cystic thyroid nodules: a single centre experience

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Introduction
Minimally-invasive management of thyroid nodules has recently garnered limelight as a treatment strategy. The first-line treatment for benign cystic and predominantly-cystic nodules with symptoms/cosmetic concerns includes aspiration, associated with high recurrence rates. This study was conducted to determine the efficacy and safety of percutaneous ethanol injection (PEI) for the treatment of cystic and predominantly-cystic thyroid nodules.
Methods
Retrospective analysis was performed of 35 patients with cystic and predominantly-cystic ($>50\%$) thyroid nodules who were treated using ultrasound-guided PEI between January 2020 to April 2022. All patients underwent fine needle aspiration (FNA) of their cyst demonstrating benign pathology (Bethesda II). The main outcomes were efficacy, defined as reduction in nodule volume of $\geq 50\%$, and safety, defined as no or minor adverse events. Patients were assessed at post-procedure months 1, 6, and 12.
Results
Thirty-five patients (32 females) underwent ultrasound-guided PEI for the treatment of cystic and predominantly-cystic thyroid nodules. Mean age was 35.6 years (19-56). All patients were euthyroid. The median largest diameter of the thyroid nodule was 4.5 cm (3.2-8.0); the median volume pre-PEI and post-PEI on last follow-up was 16.6 ml (2.6-108.1) and 3.98 ml (0.32-40) respectively. All patients had a 50% or greater reduction in nodule volume, with median volume reduction of 76% (0-97%). Three patients had recurrence. The procedure was well-tolerated by all patients. Adverse effects occurred in 4 patients (11.4%) and were mild and temporary (pain and bleeding into the cyst). The pericapsular infiltration with xylocaine pre-procedure could be the reason for less pain during and post-procedure. The injected ethanol was not reaspirated and could explain the greater volume reduction in this study.
Conclusion
Ultrasound-guided PEI appears to be a safe and effective alternative to surgical resection for patients with benign cystic and predominantly cystic thyroid nodules with pressure effects or cosmetic concerns.

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41

Non-thyroidal illness syndrome in SARS-CoV-2 infection: insights from a COVID-19 dedicated hospital at the peak of the pandemic

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Introduction
Non-Thyroidal Illness Syndrome (NTIS) is characterized by decreased serum concentration of thyroid hormones – typically free triiodothyronine (FT3). This adaptive response has been commonly observed in critically ill patients, including those with COVID-19. This study investigates the prevalence of thyroid hormone abnormalities in COVID-19 patients and their association with disease mortality.
Methods
We conducted a retrospective analysis of 846 patients hospitalized due to COVID-19 at the Regional Hospital in Słupca, wielkopolskie, Poland, between January and April 2021. We selected 137 patients, based on the availability of serum concentration measurements of thyroid-stimulating hormone (TSH), free thyroxine (FT4), FT3, and vitamin D on admission. Descriptive statistics and univariate logistic regression analysis were performed to evaluate relationship between study variables and COVID-19 mortality.
Results
Decreased levels of FT3, FT4, and TSH were observed in 21.17%, 24.82%, and 64.23% of patients. Age emerged as a significant predictor of mortality (OR = 1.07, $P = 0.014$), while TSH (OR = 0.78, $P = 0.448$), FT4 (OR = 1.69, $P = 0.385$), FT3 (OR = 0.76, $P = 0.395$), and vitamin D (OR = 1.01, $P = 0.584$) showed no significant associations.

Conclusion
We highlight the common occurrence of thyroid hormone abnormalities in the acute phase of COVID-19. However, our findings suggest that thyroid hormone concentrations do not reliably predict COVID-19 mortality, which contrasts with some previous studies. Further research is needed to explore the relationship between thyroid hormone alterations, the disease course of COVID-19, and its clinical implications.

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103

Thyroid hormones regulate the transcriptome of infiltrating microglia

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Thyroid hormones (TH) stimulate the growth of microglia cellular processes, which are reduced in hypothyroid and increased in hyperthyroid pups. However, how TH triggers its effects on these cells remains unexplored. Using confocal immunofluorescence, we have found that in the brains of postnatal day (P)5 mice, infiltrating microglia with a motile ameboid phenotype (lectin tomato and iba1 positive) exhibit strong staining of the inactivating deiodinase type 3 (D3). However, when microglia cells enter the cerebral cortex and differentiate into a sessile ramified phenotype, microglial cells did not express D3 anymore. Culture ameboid microglia (cd11b+) obtained from the brains of P5 mice express D3 at the protein and mRNA level (by RT-PCR). These exciting observations point to a new local control of TH signaling in infiltrating microglial cells, and more investigations are ongoing. We have set up a system that allows us to isolate infiltrating cd11b+ microglia from the subcortical white matter of P5 mice brains using specific microbeads. We will study the transcriptome of these cells using bulk RNA-seq and compare it to cd11b+ microglial cells obtained from P5 pups treated from P1 to P5 with either xanthohumol or triiodothyronine (T3). Next, we will isolate microglia from the transgenic thyroid hormone action indicator mouse and treat them with ATP and LPS (to promote migration or differentiation, respectively). In these cells, we will measure Dio3 mRNA levels together with luciferase (the readout of TH signaling in these mice). The involvement of the TH cell membrane transporter MCT8, is being studied using (i) super-resolution microscopy and (ii) brain organoids (wildtype and MCT8-deficient) containing microglial cells. The discovery that D3 and MCT8 are at the crossroads of the local control of TH signaling in infiltrating microglia has enormous potential for many neurodegenerative diseases and cannot be underestimated.

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126

The largest case of exophytic lymph node papillary thyroid cancer metastasis: a multidisciplinary approach from diagnosis to treatment

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Introduction
Papillary Thyroid Carcinoma (PTC), the most frequent thyroid cancer, has excellent prognosis. Risk factors for lymph node metastatic spread are capsular invasion and size >1 cm. The COVID-19 pandemic caused significant delays in thyroid cancer diagnosis due to social isolation with consequent reduced medical referral. The lack of patient examination and of ultrasonography (US) led to inadequate thyroid nodule and cancer recurrence evaluation. We hereby present, to the best of our knowledge, the largest case of exophytic lymph node PTC metastasis.
Case presentation
A 82 years old female patient living alone, come to our attention in July 2023 for a bulky exophytic, purplish, hard, warm, asymptomatic lateral neck mass. In October 2018 she was submitted to right hemithyroidectomy, isthmectomy and sentinel lymph node radioguided exeresis due to a BRAF positive PTC (T3N1Mx). Completion thyroidectomy was not performed due to right recurrent laryngeal nerve injury with right vocal cord palsy. In March 2019, US showed a 5 × 10 × 14 mm lateral neck mass consistent with recurrent disease. The patient refused completion surgery because of concomitant herpes zoster; later COVID-19 pandemic hampered any medical procedure. Contrast-enhanced CT in July 2023 showed an exophytic mass deeply attached to neck muscles next to the left submandibular gland, measuring 60 × 52 × 66 mm. Thyroglobulin, anti-thyroglobulin antibodies, TSH, FT4 were in the normal range. In September 2023, radical and demanding surgical exeresis of the mass was performed without complications. Histological diagnosis was consistent with PTC lymph node metastasis. The patient has been disease-free so far.
Conclusion
COVID-19 pandemic, in the presence of risk factors, allowed the development of a bulky PTC lymph node metastasis. Despite the advanced age and the problematic surgical management, a multidisciplinary approach allowed an excellent outcome. This case underlines the importance of seeking for solutions also in very difficult situations.

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106

Lipid profile in subclinical and overt hypothyroidism

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Introduction
The lipid metabolism is significantly influenced by thyroid hormones. It is well established that overt hypothyroidism (OH) is linked to elevated lipids; however, there is ongoing debate over its impact on subclinical hypothyroidism (SH). The aim of the study was to evaluate the association between serum lipid levels and hypothyroidism and to assess the effect of levothyroxine treatment on lipid profile.
Methods
Parametric data were tested by one way ANOVA and non-parametric data – by Kruskal Wallis test. Effect of treatment was assessed by paired t-test or Wilcoxon signed Rank test.
Results
65 patients (35 with OH, 30 with SH, and 64 healthy controls were included in the study. Total cholesterol (TC), low density lipoproteins (LDL), high density lipoproteins (HDL) were measured at baseline visit, and after 2 and 4 months of levothyroxine therapy. TC was significantly increased in OH ($P < 0.001$), but not SH ($P = 0.685$) at baseline as compared to controls. TC significantly decreased in OH (6.9±2.5 mmol/l at baseline visit, and 5.3±1.5 after 4 months of treatment, $P < 0.001$), but did not decrease in SH (5.1±1.0 mmol/l at baseline visit, 5.0±1.0 mmol/l after 4 months of treatment). Mean TC in the control group was 5.5±1.0 mmol/l. HDL significantly decreased in OH after 2 months of treatment (1.6±0.6 mmol/l and 1.3±0.3 mmol/l respectively, $P < 0.001$), but not in SH. OH also showed a significant difference in LDL before and after 4 months of treatment (4.6±2 mmol/l and 3.4±1.1 mmol/l respectively, $P = 0.001$). TSH and FT4 had a weak positive correlation with TC and LDL, but not HDL.
Conclusion
Our results indicate that compared to the general population, those with overt hypothyroidism, but not subclinical hypothyroidism, have greater levels of LDL and TC. There was a weak correlation found between lipids and FT4 and TSH.

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139

A case report thyroid storm with severe heart failure and atrial fibrillation treated by thyroidectomy after plasma exchange

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Introduction
A thyroid storm (TS) (or thyrotoxic crisis) is a rare, acute, life-threatening endocrine emergency characterized by severe clinical manifestations of thyrotoxicosis. The mortality rate is between 10 and 30%. So this condition must be quickly identified and treated by clinicians. Plasma exchange(PE) has been used as a treatment option for thyroid storms. However, to date, there have been only a few studies assessing the effect of PE with varying results.

Case Report
A 50-year-old female patient was admitted to the emergency department due to dyspnea, chest pain, and palpitations. It was learned that the patient, who had been diagnosed with hyperthyroidism for 10 years, had stopped using methimazole for 1 month. On admission, the patient's heart rate was 147. Atrial fibrillation (AF) was detected on the ECG. Echocardiography revealed EF:25-30%, global hypokinesia. The patient with TSH <0,005(0,31-4,49 mıU/l), fT4:7.77(0,85-1,70 ng/dl) fT3:11.5 (2,04-4,4 ng/l) was evaluated as thyroid storm. She was monitored in the intensive care unit. Hydrocortisone 300 mg, propylthiouracil 3*300 mg and propronolol 2*20 mg were started. Since there was not enough decrease in fT3 and fT4 levels, 3*5 drops of potassium iodide were added to the treatment. Thyroid otoanticors detected high levels. Thyroid ultrasound showed heterogeneity and focal abnormalities in the thyroid parenchyma nodüles were detected. During follow-up, hydrocortisone was switched to methylprednisolone, and propylthiouracil was switched to methimazole. In the consultation with the general surgeon, a thyroidectomy was planned to be performed after plasmapheresis for the patient who did not have a sufficient decrease in fT3 and fT4. The patient underwent plasmapheresis for 3 days. After plasmapheresis fT3 decreased from 5,27 to 4,1 and fT4 decreased from 2,96 to 2,4. Thyroidectomy was performed. Control echocardiography EF was seen as 50-55% and the peak HR was between 70-80. Ft3:0,4 fT4:0,26 was observed and levothyroxine was started. Cardiology planned to perform cardioversion on the patient whose AF rhythm continued was planned to continue outpatient follow-up with cardiology.
Conclusion
PE is a treatment option for thyroid storm. However, the effect of PE has not been accurately assessed yet. So we think that more case reports are needed.

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161

Therapeutic plasma exchange as a bridge to radioactive iodine treatment in a patient with severe thyrotoxicosis and serious adverse effects to antithyroid drugs: a case report

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Introduction
Thyrotoxicosis is a clinical state of inappropriately high levels of circulating thyroid hormones (TH), most commonly caused by Graves' disease (GD). First line treatment includes antithyroid drugs (ATD). Complications such as agranulocytosis could limit their use, leaving radioactive iodine treatment (RIT) as a treatment of choice.
Case presentation
A 67-year-old woman was admitted for severe thyrotoxicosis (TSH <0.01 mIU/l, FT4 52.2 pmol/l, FT3 11.2 pmol/l, anti-TSH receptor antibodies, TRAb 12.6 IU/l, ref. range <1.75). Her past medical history was remarkable for GD. She was previously initially treated with methimazole, replaced later with propylthiouracil (PTU) due to the development of urticaria. On admission she was given 300 mg of PTU with high doses of propranolol. On the second day of hospitalization, agranulocytosis was developed, which lead to cessation of PTU and initiation of supportive and symptomatic treatment. Propranolol at a dose of 160 mg/day and oral prednisone increasing the dose up to 80 mg/day were administrated, but unfortunately with no response. Thus, considering the high free fractions of TH (FT4 57.5 pmol/l, FT3 23.3 pmol/l) and TRAb 15.7 IU/l, it was decided to perform therapeutic plasma exchange (TPE), in order to prevent complications and improve the thyroid hormonal status before referring to RIT. Two TPEs were performed in 3 days. Significant improvement was noted in the thyroid hormonal status (FT4 31.4 pmol/l, FT3 7.1 pmol/l, TRAb 4.93 IU/l) and patient's general condition. RIT was subsequently applied, and after month and a half normalization of FT4 17.0 pmol/l and FT3 3.6 pmol/l was achieved with lower TRAb 2.30 IU/l.
Conclusion
TPE is not currently recommended for the treatment of hyperthyroidism, but in severe cases where ATD are contraindicated or ineffective, TPE may be initiated as bridge therapy to RIT or thyroidectomy.

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