belgian endocrine society

30th meeting of the
Belgian Endocrine Society

Saturday 17 October 2020

Virtual meeting

ABSTRACT BOOK

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Program

9:00-9:15 General assembly

Brigitte Velkeniers (VUB), President

9:15 Communications by young investigators (sponsored by Pfizer)

Introduced by Patrick Petrossians (ULiège)

9:15-10:30 Part 1: Translational and clinical studies

- Intestinal delivery of proinsulin and IL-10 via Lactococcus latis combined with low-dose antiCD3 induces antigen-specific FoxP3+ Tregs in autoimmune diabetic mice.
  Pieter-Jan Martens (KUL)
- YIPF5 mutations cause diabetes and microcephaly through disrupted endoplasmic reticulum-to-Golgi trafficking.
  Maria Lytrivi (ULB)
- Sexual symptoms predict all-cause mortality independently of sex steroids in ageing men.
  Leen Antonio (KUL)
- Soft drink intake on time of hypoglycaemia during insulin tolerance test: effects on pituitary response and comfort for the patient.
  Coralie Thiry (ULB)
- Chronic complications versus glycaemic variability, time in range and HbA1c in people with type 1 diabetes: sub study of the RESCUE-trial.
  Anass El Malahi (UAntwerp)

10:30-11:00 Part 2: Clinical case reports

- An unusual cause of unilateral adrenal incidentaloma.
  Younes Azzagnuni (ULB)
- A case of a heterozygous inactivating CASR variant with adult-onset symptomatic hypercalcemia requiring extensive surgery.
  Laurens Veldeman (UGent)

11:00-11:05 *Short break*

11:05-11:20 Selected Belgian Publication Award (sponsored by Sandoz)
Introduced by Brigitte Velkeniers (VUB), President

Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. :
Clara Depommier (UCL)

11:20-11:50 Belgian Endocrine Society Lecture Award (sponsored by Novo Nordisk)
Introduced by Brigitte Velkeniers (VUB), President

Advanced therapies that improve glucose control and quality of life of people with type 1 diabetes.
Award winner: Pieter Gillard (KUL)

11:50 *Farewell*

Abstracts BES 2020

The abstracts will be published online, as a Volume of Endocrine Abstracts in html and as a downloadable PDF.

TRANSLATIONAL STUDIES

Dimerization of the ligand-binding domain is crucial for proper functioning of the androgen receptor

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The importance of the androgen receptor (AR) in the development and maintenance of the male phenotype is demonstrated by patients with androgen insensitivity syndrome (AIS). These patients carry germline mutations in the AR and display a mild to complete intersex phenotype. The AR belongs to the subfamily of steroid receptors, which need to form homodimers to execute their role as transcription factors. For estrogen receptors, dimerization via the DNA-binding domains as well as via the ligand-binding domains (LBDs) is well documented. For the AR, however, LBD dimerization has only recently been identified by means of a crystal structure of AR LBDs. In *in vitro* assays, AR LBD dimerization was agonist-dependent and inhibited by androgen antagonists. We also showed that some AIS mutations in the AR LBD indeed disrupt this dimerization interface. A clear example is the W752R mutation, found in two siblings with AIS but information about the severity of their phenotype is lacking (1). *In vitro*, this mutation was still able to induce androgen reporter genes albeit at higher hormone concentrations.

To study the physiological relevance of AR LBD dimerization, we introduced the corresponding mutation (W731R) by CRISPR/Cas9 into the germ line of mice. The thus generated $AR^{Lmon/Y}$ males have an external female phenotype with small, cryptorchid testes, yet high circulating levels of testosterone, androstenedione and LH. Prostate, seminal vesicles and epididymis did not develop. Despite the elevated testosterone levels, the $AR^{Lmon/Y}$ mice have a severe bone phenotype, similar to the bone phenotype of complete AR knockout (ARKO) mice. Because the $AR^{Lmon/Y}$ mice have high circulating levels of testosterone, which can still function as prohormone for estradiol, this observation suggests a direct effect of the AR on bone homeostasis. Heterozygous $AR^{Lmon/X}$ female mice had normal fertility, number of litters and pups per litter.

Transcriptomic and immunohistological analysis of the $AR^{Lmon/Y}$ testes showed hyperplasia of the Leydig cells, presence of Sertoli cells and residual spermatogenesis. The AR responses

where completely absent in Leydig and Sertoli cells as well as in other androgen-responsive organs. Indeed, castration experiments with supraphysiological testosterone replacement confirmed absence of androgen response in $AR^{Lmon/Y}$ kidneys while AR regulation was observed in wild type kidneys. Furthermore, analysis of the steroidogenic pathway revealed that the expression of *Hsd17b3,* which is responsible for the conversion of androstenedione into testosterone, is low in $AR^{Lmon/Y}$ testis. Reporter assays demonstrated that the transcription of this gene is regulated by the AR itself.

In conclusion, the $AR^{Lmon/Y}$ mouse model reveals the physiological importance of LBD dimerization of the AR. This is the first report of a mouse model with a disrupted LBD dimerization of a steroid receptor.

1. Boehmer AL*, et al.* (2001) Genotype versus phenotype in families with androgen insensitivity syndrome. *J Clin Endocrinol Metab* 86(9):4151-4160.

Novel model of sex steroid deficiency in mice to study the physiological effects of delayed and suppressed puberty

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[$] Contributed equally as last authors

Background: Sex steroids are critical for skeletal development and maturation during puberty as well as skeletal maintenance during adult life. However, the exact time during puberty when sex steroids have the highest impact as well as the ability of bone to recover from transient sex steroid deficiency is unclear. The latter is highly relevant in the clinical context of delayed puberty, since the impact of a delayed pubertal onset on adult bone health remains elusive. Surgical castration is a common technique to study sex steroid effects in rodents, but it is irreversible, invasive, and associated with metabolic and behavioral alterations. Hence, alternative approaches are needed to study timing and reversibility of sex steroid actions.

Methodology: We used a low dose (LD) or a high dose (HD) of gonadotropin-releasing hormone antagonist to either temporarily or persistently suppress sex steroid action in male mice, respectively. Growth, body composition and bone parameters were determined.

Results: The LD group, a model for delayed puberty, did not show changes in linear growth or body composition, but displayed reduced trabecular bone volume during puberty, which fully caught up at adult age. In contrast, the HD group, representing complete pubertal suppression, showed a phenotype reminiscent of that observed in surgically castrated rodents. Indeed, HD animals exhibited severely impaired cortical and trabecular bone acquisition, decreased body weight and lean mass, and increased fat mass. In addition, the HD group was characterized by an increased linear growth, which is reminiscent of the clinical observation in patients with hypogonadotropic hypogonadism.

Conclusions: We validated a new rodent model of chemical castration, which can be used as an alternative to surgical castration. Moreover, the transient nature of the intervention enables to study the effects of delayed puberty and reversibility of sex steroid deficiency. Our work suggests that, at least in mice, a delayed pubertal timing is associated with bone loss during puberty but this deleterious effect does not persist at adult age.

YIPF5 mutations cause diabetes and microcephaly through disrupted endoplasmic reticulum-to-Golgi trafficking
Category: translational research

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Objective: Neonatal diabetes is caused by single gene mutations reducing pancreatic β-cell number or impairing β-cell function. Understanding the genetic underpinnings of rare diabetes subtypes highlights fundamental biological processes in β-cells. Our aim was to explore the genetic basis of a syndrome characterized by neonatal diabetes, microcephaly and epilepsy.

Methods: We performed whole genome sequencing for 2 unrelated patients with neonatal diabetes (diagnosed aged 5 and 9 weeks), born to consanguineous parents. Replication studies were performed in 187 patients with early-onset diabetes by a targeted next generation sequencing assay. We used three human β-cell models (*YIPF5* silencing in EndoC-βH1 cells, *YIPF5* knock-out and mutation knock-in in embryonic stem cells, and patient-derived induced pluripotent stem cells) to investigate the mechanism through which *YIPF5* loss-of-function affects β-cells. Results: We identified 6 patients from 5 families with homozygous mutations in the *YIPF5* gene, which is involved in endoplasmic reticulum (ER)-to-Golgi trafficking. All patients had neonatal/early-onset diabetes, severe microcephaly and epilepsy. *YIPF5* is expressed during human brain development, in adult brain and pancreatic islets. Loss of *YIPF5* function in stem cell-derived islet cells resulted in proinsulin retention in the ER, marked ER stress and β-cell failure. Partial *YIPF5* silencing in EndoC-βH1 cells and a patient mutation in stem cells increased the β-cell sensitivity to ER stress-induced apoptosis.

Conclusions: We report recessive *YIPF5* mutations as the genetic cause of a novel syndrome of microcephaly, epilepsy and neonatal/early-onset diabetes, highlighting a critical role of *YIPF5* in β-cells and neurons. This is the first report of mutations disrupting the ER-to-Golgi trafficking resulting in diabetes.

Intestinal delivery of proinsulin and IL-10 via *Lactococcus lactis* combined with low-dose antiCD3 induces antigen-specific FoxP3+ Tregs in autoimmune diabetic mice

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Background and aims: An interesting approach in the pursuit for a cure of type 1 diabetes is restoration of immune tolerance by a combination treatment of low-dose aCD3 with the islet antigen proinsulin (PINS) and the pro-tolerogenic cytokine IL-10 administered orally via genetically modified *Lactococcus lactis (L. lactis)* bacteria. The purpose of adding PINS is to expand antigen-specific Tregs as they are believed to migrate preferentially to disease-related target organs and be more powerful in dampening overactive immune responses. The **aim of this study** is to prove antigen-specificity of the *L. lactis*-based antigen immunotherapy.

Materials and methods: Newly diagnosed diabetic NOD mice were injected with alloxan (90 mg/kg i.v., Sigma) in order to completely deplete residual endogenous beta cell mass. After 48 hours, all mice received 500 insulitis-free syngeneic islets and were either 1) left untreated (CTRL), 2) treated with aCD3 alone (aCD3), 3) aCD3 combined with *L. lactis* bacteria secreting PINS with IL-10 (CT), or 4) aCD3 combined with *L. lactis* secreting a non-islet antigen, ovalbumin with IL-10 (aCD3+LL-OVA). Flow cytometry analysis was done with insulin-reactive (e.g., InsB12-20 (TEGVEALYLVC-GGGS) and InsB13-21 (TEGEALYLVCGEGGS) PE- and APC-labeled MHC/peptide tetramers, used at a final concentration of 10 mg/ml in FACS buffer for 1 hour at room temperature.

Results: The CT providing proinsulin protected 69% of mice, compared to 33% when an irrelevant antigen (OVA) was combined with aCD3 therapy, or to 27% with aCD3 therapy alone. Flow cytometry data indicate that Foxp3+ Tregs, both CD25- and CD25+, in the islet grafts of mice, treated with aCD3 combined with *L. lactis* secreting PINS and IL-10, contained significantly more InsB12-20+ cells compared to those in the islet grafts of mice under anti-CD3 (with or without OVA) therapy alone or the untreated controls (Figure 1). Interestingly, increased numbers of Foxp3+ Tregs detected in the islet grafts of the combination therapy-treated mice were reactive to InsB12-20 and less to InsB13-21 (data not shown). Only in the mice treated with the add-on of the islet antigen proinsulin, a higher degree of insulin-reactive Tregs in the islet grafts was observed. Moreover, these insulin-reactive Tregs were preferentially observed in the islet grafts but not in the kidney draining lymph nodes (KLN) (**Figure 1**), indicating that these cells trafficked to the inflammatory sites where they may suppress persistent effector T cell function.

Conclusion: This study provides for the first time strong evidence for the antigen specificity of our *L. lactis*-based antigen immunotherapy as PINS was needed for Foxp3+ Tregs to become insulin-reactive and home to insulin-containing islet grafts.

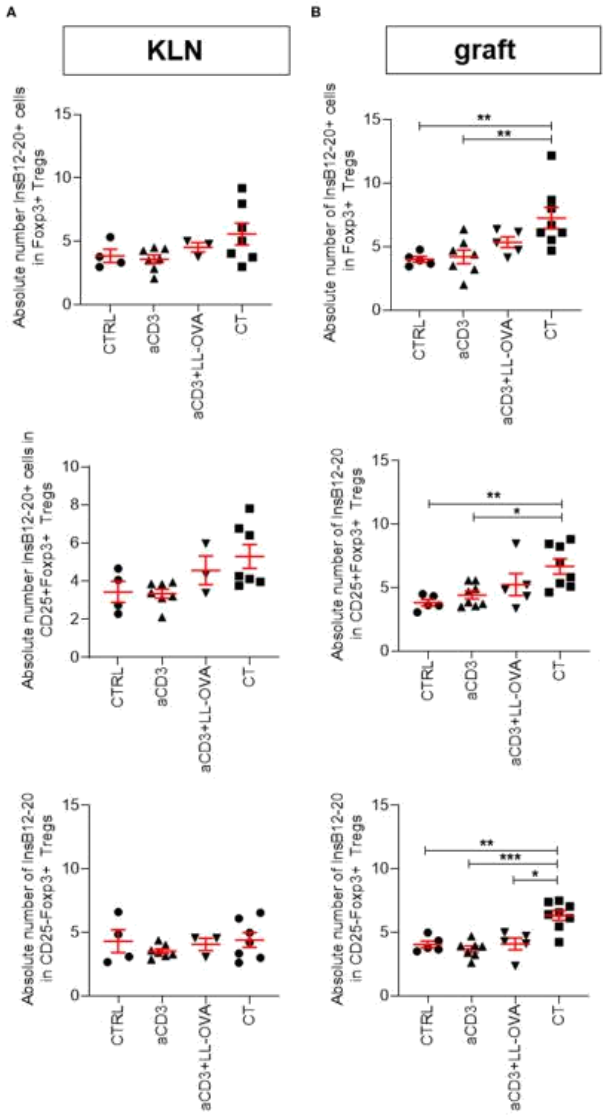

Figure 1. Combination therapy increases numbers of InsB12–20^{+}Foxp3^{+}CD4^{+} T cells in islet grafts. Newly diagnosed diabetic NOD mice with disease duration of <2 days were injected i.v. with alloxan (90 mg/kg) and transplanted with 500 syngeneic islets after 48 h. Mice were left untreated (CTRL; *n* = 4–5) or given a short-term low-dose aCD3 therapy (aCD3; *n* = 7–8) either alone or combined with *L. lactis* bacteria secreting the irrelevant antigen ovalbumin (LL-OVA; *n* = 3–5) or secreting beta cell antigen (PINS; *n* = 7–8) combined with IL-10 (CT). Absolute numbers of tetramer positive (tet+) InsB12–20 cells per 100 Foxp3+ Tregs, either CD25+ or CD25−,are shown 3 weeks after islet substitution and therapy initiation in the kidney draining lymph nodes (KLN) (A) and islet grafts (B) of diabetic NOD mice. Symbols represent individual mice, and line and error bars reflect group mean ± SEM. Statistical significance between groups was calculated by Mann-Whitney U test; *P < 0.05, **P < 0.01, ***P < 0.001.

Purification of pancreatic endocrine subsets reveals increased iron metabolism in beta-cells

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Objectives: The main endocrine cell types in pancreatic islets are alpha-, beta-, and delta-cells. Although these cell types have distinct roles in the regulation of glucose homeostasis, inadequate purification methods preclude the study of cell-type-specific effects. We aimed to develop a reliable approach that enables simultaneous sorting of live alpha-, beta-, and delta-cells from mouse islets for downstream analyses.

Methods: We developed an antibody-panel against cell-surface antigens to enable isolation of highly purified endocrine subsets from mouse islets, based on specific differential expression of CD71 on beta-cells and CD24 on delta-cells. We rigorously demonstrate the reliability and validity of our approach using bulk and single-cell qPCR, immunocytochemistry, reporter mice, and transcriptomics.

Results: Pancreatic alpha-, beta-, and delta-cells can be separated based on beta-cell-specific CD71 surface expression and high expression of CD24 on delta cells. We applied our new sorting strategy to demonstrate that CD71, which is the transferrin receptor mediating the uptake of transferrin-bound iron, is upregulated in beta-cells during early postnatal weeks. We find that beta-cells express higher levels of several other genes implicated in iron metabolism, and that iron deprivation significantly impairs beta-cell function. In human beta-cells, CD71 is similarly required for iron-uptake and CD71 surface expression is regulated in a glucose-dependent manner.

Conclusions: This study provides a novel and efficient purification method for murine alpha-, beta-, and delta-cells, identifies for the first time CD71 as a post-natal beta-cell-specific marker, and points to a central role for iron metabolism in beta-cell function.

CLINICAL STUDIES

Sexual symptoms predict all-cause mortality independently of sex steroids in ageing men

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Background: The association between low testosterone (T) and higher mortality in men remains controversial. Most studies focus only on the association between total T (TT) and mortality. While TT declines with age, free T (FT) shows a greater fall, due to the rise in SHBG. Moreover, also sexual dysfunction, often co-existing with low T, has been associated with mortality in ageing men.

Objective: To study the interrelationships between sex steroids and sexual symptoms with all-cause mortality in a large prospective cohort of European men.

Methods: 1913 community-dwelling men, aged 40-79, participated in the European Male Ageing Study (EMAS) between 2003-2005. Sexual symptoms were assessed via a validated questionnaire (EMAS-SFQ). Sex steroids were measured by mass spectrometry. In 5 of 8 EMAS centres, survival status was available until April 2018. Cox proportional hazard models were used to study the association between hormones, sexual symptoms and mortality. Because of the wide age range at study entry, age was used as time-scale, instead of years since inclusion adjusting for age. Results were expressed as hazard ratios (HR) with 95% confidence intervals, adjusted for centre, BMI and smoking.

Results: 483 (25.3%) men died during a mean follow-up of 12.4±3.3 years. Men who died had a higher BMI (p=0.002), but smoking status did not differ. TT levels were similar in both groups, but FT was lower in those who died (mean±SD: 312±86 pmol/L vs 270±84, p<0.001) and LH was higher (5.7±3.3 U/L vs 7.8±5.8, p<0.001).

Men in the lowest FT quartile had higher mortality risk compared to men in the highest quartile (HR 1.43 (1.06-1.95); p=0.021). Also men in the highest FSH quartile had increased mortality risk (HR 1.38 (1.02-1.88); p=0.036). However, there was no association with TT, E2 or LH.

Men with 3 sexual symptoms had a higher mortality risk compared to men with no sexual symptoms (HR 1.77 (1.28-2.41); p<0.001). In particular erectile dysfunction and poor morning erections, but not lower libido, were associated with increased mortality (HR 1.40 (1.15-1.73); p=0.001; HR 1.30 (1.06-1.60); p=0.012; HR 1.14 (0.93-1.40); p=0.203 respectively). Further adjusting for TT and FT did not influence the observed HRs. Also in men with normal TT (>12 nmol/L), the presence of sexual symptoms increased mortality risk (HR 1.51 (1.15-1.97); p=0.003). Finally, men with TT<8 nmol/L and sexual symptoms had a higher mortality risk compared to men with normal TT and no sexual symptoms (HR 1.92 (1.05 - 3.52); p=0.035).

Conclusions: Men with the lowest FT and highest FSH levels have an increased mortality risk. Sexual symptoms, in particular erectile dysfunction, predict all-cause mortality independently of T levels. As both vascular disease and low T can influence erectile function, sexual symptoms can be an early sign for increased cardiovascular risk and mortality.

Early decline of androgen levels in healthy adult men: an effect of aging *per se*? A prospective cohort study.

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[2]Department of Clinical Chemistry, Ghent University Hospital, Ghent, Belgium.

Background: Investigating longitudinal changes in serum androgen levels in healthy men in relation to (changes in) body composition, lifestyle factors and intercurrent illnesses.

Methods: Longitudinal observational study. 999 healthy men aged 24-46 years of whom 691 were re-evaluated after a mean period of 12 years. Serum SHBG, luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels were measured using immuno-assays. Testosterone (T), estradiol (E2), dihydro-testosterone (DHT), androstenedione (Adione) were measured using LC-MS/MS, free T was calculated (cFT). Analyses adjusted for age, (changes in) BMI, lifestyle factors and intercurrent illnesses.

Findings: Baseline age was 34±6 years. Mean BMI increased by 1.19kg/m², T levels decreased by 14.2% (20.78 nmol/l vs 17.84 nmol/l), cFT by 19.1% (392.14 pmol/l vs 317.33 pmol/l), DHT by

15.6% (1.54nmol/l vs. 1.30nmol/l), and Adione by 10.7% (3.72nmol/l vs 3.32nmol/l; all $p<0.001$). E2 did not change over time ($p>0.05$). SHBG increased by 3.0% (39.8nmol/l vs 41.04nmol/l), LH by 5.8% (4.57U/l vs 4.85U/l) and FSH by 14.7% (4.31U/l vs. 5.05U/l) (all $p<0.001$). For T, cFT, DHT, Adione and SHBG these longitudinal changes persisted after adjustment for confounders (all $p<0.001$).

Interpretation: Serum androgen levels start declining early during adult life and independently from changes in BMI and other lifestyle factors, suggesting that aging per se leads to an altered sex steroid status. Given the concurrent rise in gonadotropin levels, the decline in androgen status most likely arises from primary decrease in testicular function.

Funding: This study was supported by a grant from the Fund for Scientific Research – Flanders (FWO-Vlaanderen, Grant #G.0876.11).

Influence of diabetes knowledge and health literacy on metabolic control in adults with type 1 diabetes starting with intermittently scanned continuour glucose monitoring: the FUTURE-PEAK trial.

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(*) shared first authorship

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Objective – Nation-wide reimbursement of intermittently scanned continuous glucose monitoring (isCGM) for people with type 1 diabetes was introduced in Belgium in 2016. We investigated whether diabetes knowledge and health literacy would impact glycemic control after one year of isCGM use.

Research design and methods – In this substudy of the FUTURE trial, a prospective observational real-world cohort study in individuals with type 1 diabetes ≥16 years old, we assessed diabetes knowledge using a new 10-item questionnaire (Patient Education And Knowledge [PEAK]) and health literacy using the validated 6-item Newest-Vital Sign-D (NVS-D) questionnaire. Primary outcome measure was the association between PEAK score and change in HbA1c. Secondary outcome measures were the association between the NVS-D score and change in HbA1c, the link between time spent in/above/below range and scores on the PEAK/NVS-D questionnaires.

Results – 851 subjects were consecutively recruited between July 2016 and July 2018. Median PEAK score was 8 (range: 0-10) and median NVS-D score was 6 (range 0-6). HbA1c improved from 7.9 [7.8; 8.0]%, 63 [62; 64] mmol/mol at start to 7.7 [7.6; 7.7]%, 61 [60; 61] mmol/mol ($p<0.001$) at 6 months and to 7.8 [7.7; 7.9]%, 62 [61, 63] at 12 months ($p<0.001$). Time spent <70 mg/dl and <54 mg/dl were reduced by respectively 15% (from 9.6 [9.1; 10.1]% to 8.2 [7.8; 8.7]%, $p<0.001$) and 14% (from 4.2 [3.9; 4.5]% to 3.6 [3.4; 3.9]%, $p<0.001$) after 12 months. Time spent >180 mg/dl was increased during the study period by 6% after 12 months (from 37.7 [36.6; 38.9]% to 39.9 [38.7; 41.1]%, $p<0.001$). HbA1c only improved in those with higher scores on PEAK score (PEAK score 7-8: from 8.0 [7.8; 8.2]%, 64 [62, 66] mmol/mol to 7.7 [7.5; 7.8]%, 61 [58, 62] mmol/mol at 12 months, $p=0.005$; PEAK score 9-10: 7.9 [7.7; 8.1]%, 63 [61, 65] mmol/mol) to 7.7 [7.6; 7.8]%, 61 [60, 62] mmol/mol) at 12 months, $p<0.001$) and NVS-D questionnaires (NVS-D score 4-6: 7.9 [7.8; 8.0]%, 63 [62, 64] mmol/mol) to 7.7 [7.6; 7.8]%, 61 [60, 62] mmol/mol) at 12 months, $p<0.001$)

Time spent >180 mg/dl increased in those with the lowest score on the NVS-D questionnaire (from 38.4 [35.3; 41.5]% to 41.8 [38.4: 45.3]%, $p=0.042$).

Conclusions – In this large cohort of well-educated adults with type 1 diabetes, use of isCGM resulted in an improvement in HbA1c and a reduction of time in hypoglycemia. However, HbA1c only improved in those with higher scores on the PEAK/NVS-D questionnaires, pointing towards the importance of diabetes knowledge and health literacy.

Sex differences in association between gestational weight gain and neonatal adiposity: boys are at higher risk

Running title: sex differences in neonatal adiposity

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Aims: To determine predictors of neonatal adiposity and differences in associations by fetal sex in women with gestational diabetes mellitus (GDM), normal-weight and overweight (BMI ≥25 Kg/m²) normal glucose tolerant women (NGT).

Methods: Skinfold thickness was measured in 576 newborns, and cord blood leptin, c-peptide and lipids in 327 newborns in a multi-centric prospective cohort study.

Results: Compared to neonates of normal-weight NGT women (327), neonates of women with GDM (97) were at higher risk of being large-for-gestational age (LGA) (16.5% vs 8.6%, p=0.024) but the macrosomia rate (8.2% vs 5.8%, pp=0.388), sum of skinfolds (13.9mm±2.9 vs 13.3mm±2.6,p=0.067), neonatal fat mass (1333.0g±166.8 vs 1307.3g±160.9, p=0.356), and cord blood biomarkers were not significantly different. Compared to neonates of normal-weight NGT women, neonates of overweight NGT women (152) had higher rates of macrosomia (12.5% vs 5.8%, p=0.012), LGA (17.1% vs 8.6%, p=0.006), higher sum of skinfolds (14.3mm±2.6 vs 13.2mm±2.6, p<0.001), neonatal fat mass (1386.0g±168.6 vs 1307.3g±160.9, p<0.001), % neonatal fat mass >90Th percentile (15.2% vs 7.1%, p<0.001), without significant differences in cord blood biomarkers. Maternal BMI, fasting glycaemia, insulin resistance, triglycerides, gestational weight gain, cord blood leptin and cord blood triglycerides were independent predictors for neonatal adiposity. Gestational weight gain was positively associated with adiposity in boys only.

Conclusions: Compared to neonates of normal-weight NGT women, neonates of GDM women have higher LGA rates but similar adiposity, while neonates of overweight NGT women have increased adiposity. Limiting gestational weight gain might be especially important in the male fetus to reduce neonatal adiposity.

Vaginal bleeding and spotting in transgender men after initiation of testosterone therapy: A prospective cohort study (ENIGI)

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Background: Previous cross-sectional studies have described amenorrhea in cohorts of transgender men on intramuscular or subcutaneous testosterone injections. It remains uncertain which testosterone preparations most effectively suppress vaginal bleeding and when amenorrhea occurs after testosterone initiation.

Aim: To investigate the clinical effects of various testosterone preparations on vaginal bleeding and spotting in transgender men.

Methods: This prospective cohort study was part of the European Network for the Investigation of Gender Incongruence (ENIGI). Data on the persistence and intensity of vaginal bleeding and spotting, serum sex steroid levels and body composition were both prospectively and cross-sectionally assessed in 267 transgender men during a three-year follow-up period, starting at the initiation of various testosterone preparations.

Results: After 3 months of testosterone, 17.9% of transgender men reported persistent vaginal bleeding and 26.8% reported spotting. The percentages reporting vaginal bleeding and spotting decreased over the first year of testosterone (bleeding 4.7% and spotting 6.9% at 12 months, respectively), with no participants reporting vaginal bleeding or spotting after 18 months of testosterone.

Factors associated with persisting vaginal bleeding or spotting included lower serum testosterone levels and being on testosterone gel as compared to injections (e.g., esters or undecanoate preparations).

If vaginal bleeding continued, starting progestogens at 3 months resulted in a cessation of vaginal bleeding and a decrease in the intensity of spotting within the next 3 to 6 months.

Discussion: Transgender men and hormone-prescribing providers can be reassured that vaginal bleeding and spotting usually stop within 3 months after testosterone initiation. If not, serum testosterone levels should be measured and testosterone dose adjusted to achieve serum testosterone levels in the physiologic male range. Adding a progestin can be considered after 3 to 6 months if bleeding persists. Providers should be aware that cessation of bleeding can be more difficult to achieve in transgender men with lower serum testosterone levels or those on testosterone gel.

Multiple endocrine neoplasia type 1: a single center-based series

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Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disease caused by mutations in the *MEN1* gene (a tumor supressor gene) leading to the development of endocrine and non-endocrine tumours with variable penetrance.

The most frequent features are primary hyperparathyroidism, duodeno pancreatic endocrine tumours and pituitary adenomas.

Aim of the work

The aim of this retrospective study was to establish the prevalence and characteristics of multiple endocrine neoplasia type 1 patients followed at the University Hospital of Liege these last 35 years.

Methods

We studied the data of 50 MEN1 patients from 15 families, followed or diagnosed in our center between 1985 and 2020. We collected data regarding the mutations, the types of tumours, their clinical presentation and the treatments administered.

Results

In our MEN1 series, 41 (82%) patients were *MEN1* mutation positive, and 9 (18%) were *MEN1* mutation negative. The mutation-negative cases were diagnosed at an older age (59 vs 33 years, p= 0.018) and had only two of the three major conditions associated with MEN1.

None of them had *CDKN1B* mutation.

Primary hyperparathyroidism was the most frequent manifestation and occurred in 38 of 50 patient (81%). It was the first clinical manifestation of the disease in 17 patients (37.8%). Ultrasonography was able to locate abnormal parathyroid glands in 76% of cases.

Primary hyperparathyroid was most commonly induced by multiglandular hyperplasia (approximately 64%). Eighty percent of patients had damage of the target organs, mainly osteopenia/osteoporosis. Surgery was performed in 27 patients (71%) with 11 relapses (44%).

The second most frequent lesion was duodeno-pancreatic involvement (70% of cases, n = 35) predominantly manifesting as nonfunctional tumours (56 %).

Pituitary adenomas were found in 23 patients (52%). Fifty percent of these tumors were macroadenomas. There were 12 prolactinomas, 6 nonsecreting tumors, 2 gonadotrophinomas, 1 Somatotrophinoma, 1 somatomammotrope adenoma and 1 with insufficient data.

Adrenal enlargement was reported in 7 patients (17%) with hormonal hypersecretion in 1 case (primary hyperaldosteronism).

Six patients developed “carcinoid” tumours: 2 bronchial, 2 thymic and 2 gastric.

Conclusions

In our series, 9 patients (18%) were *MEN1* mutation negative. The patients with MEN1-associated tumors but without *MEN1* mutations may represent phenocopies or have mutations involving other genes.

The tumors encountered in multiple endocrine neoplasia type 1 differ from their sporadic forms in many ways. Primary hyperparathyroidism occurs earlier and is associated with pluriglandular hyperplasia in about 60 % of cases. Ultrasonography was able to locate abnormal parathyroid glands in 76% of cases while the reported sensitivity of conventional ultrasonography for localization ranges from 49% to 89%.

In our MEN1 series, the risk of recurrence of hyperparathyroidism was the same regardless of the type of surgery (subtotal vs adenomectomy), the histological nature (adenoma vs hyperplasia) and the finding of *MEN1* mutations.

Pituitary adenomas were generally larger than their sporadic forms and were frequently prolactinomas. They had developped at a younger age when compared to sporadic pituitary adenomas.

Early diagnosis of MEN1 syndrome is essential in order to set up specific monitoring and early intervention, limiting the risk of abnormal hormone secretion and malignant progression.

Chronic complications versus glycaemic variability, time in range and HbA_{1c} in people with type 1 diabetes: sub study of the RESCUE-trial

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Background and aims: So far, HbA1c is the only metric of glucose control showing a strong association with chronic complications. However, it does not reflect short-term glycemic variability nor provides guidance in decreasing risk of hypoglycemia. More widespread use of continuous glucose monitoring (CGM) has changed the way people with type 1 diabetes (T1D) manage their glycemia by providing information about glycemic variability and time spent in different glucose ranges.

Materials and methods: Parameters that could have a link with diabetes complications were analyzed of 515 adults with T1D who entered the Belgian reimbursement system for real-time CGM (rtCGM): HbA1c, standard deviation (SD), coefficient of variation (%CV), time in range (TIR, 70-180 mg/dL), age, diabetes duration, BMI, and gender. Association between glucometrics from the first 2 weeks of rtCGM use and presence of the following diabetes complications at start were investigated with multiple logistic regression: composite microvascular complications (defined as presence of at least 1 of the following: peripheral or autonomic neuropathy, retinopathy, nephropathy), macrovascular complications, and hospitalization for hypoglycemia and ketoacidosis.

Results: Diabetes duration (OR=1.12, P<0.001) and TIR (OR=0.97, P=0.005) were independently correlated with composite microvascular complications. For nephropathy, diabetes duration (OR=1.08, P<0.001) and HbA1c (OR=1.65, P=0.012) were independently associated. For retinopathy it were diabetes duration (OR=1.14, P<0.001) and TIR (OR=0.96, P<0.001). For peripheral and autonomic neuropathy it were diabetes duration (OR=1.09, P<0.001; OR=1.08, P<0.001) and SD (OR=1.03, P=0.026; OR=1.035, P=0.015). Age (OR=1.08, P=0.003) and HbA1c (OR=1.80, P=0.044) were independently correlated with macrovascular complications. Only TIR (OR=0.97, P=0.021) was independently associated with hospitalization for hypoglycemia or ketoacidosis.

Conclusion: Shorter TIR was associated with the presence of composite microvascular complications, and with retinopathy in particular. A higher SD was linked to peripheral and autonomic neuropathy. For hospitalization due to hypoglycemia or ketoacidosis, TIR was the most important factor.

Bone impact of long-term replacement therapy with recombinant human parathyroid hormone (1-34) in adult patients with hypoparathyroidism evaluated by bone scintigraphy

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Introduction: recombinant human parathyroid hormone (rPTH) (1-34) is prescribed off-label in France for patients with hypoparathyroidism resistant to conventional therapy. However, the bone impact of this long-term replacement therapy is not well known.

Objective: To determine the skeletal impact of chronic treatment with rPTH (1-34) in patients with hypoparathyroidism.

Design: Single-center prospective study. Patients treated for more than 2 years underwent Tc-99m MDP bone scintigraphy with early whole body image.

Results: 25 patients were treated with rPTH (1-34) for a median duration of 29 [IQR 25-75: 12 - 60.5] months. Median serum calcium was 2.08 [IQR 25-75: 2 - 2.21] mmol / L, indicative of a good calcium control. Seventeen patients received rPTH (1-34) for more than 2 years, 4 of whom developed diffuse osteo-articular pain. Bone scintigraphy, performed in 14 patients, revealed in 7 (50%) patients a bone hyperfixation evoking a "super bone scan" usually seen in hyperparathyroidism. Bone hypermetabolism was not associated with pain but was accompanied by an increase in alkaline phosphatase ($p < 0.05$). In 3 patients, treatment was stopped and the bone scan returned to normal after one year.

Conclusions: Long-term treatment with rPTH (1-34) may induce abnormal stimulation of bone cells despite an adequate control of hypocalcaemia, possibly due to the pharmacokinetics of the drug. Bone scintigraphy may be useful in detecting iatrogenic hyperparathyroidism in patients receiving long-term rhPTH (1-34).

Influence of catecholamine secretory phenotype and preoperative alpha-blocker preparation on surgical outcome in pheochromocytoma

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Objectives: Surgery of pheochromocytomas (PC) still carries a high risk of hemodynamic complications during the perioperative period. We aimed to evaluate the influence of their secretory phenotype and preoperative alpha-blocker treatment on surgical outcome.

Design: a retrospective monocentric study at a tertiary medical center.

Patients: 80 consecutive patients operated for an adrenal PC between 1988 and 2018.

Results: Initial diagnosis of PC was based on typical symptoms and signs in 72% of patients, genetic testing in 16% and work-up of an adrenal incidentaloma in 12%. A genetic predisposition was however found in 34% of index cases. Most patients (78/80) were cured by surgery but a relapse of the tumor was observed in 5 cases, after a median delay of more than 10 years, and malignant behavior was observed in 7 (9%). About 92% of the patients had a secreting PC; more than 2/3 had an adrenergic phenotype and less than 1/3 a noradrenergic phenotype. Biochemically silent PCs (n=6) were asymptomatic and of smaller size, while noradrenergic tumors were the largest ones but did not significantly differ in their clinical presentation compared with adrenergic PCs. Regarding outcome, the rate of peroperative hemodynamic complications was not influenced by the secretory phenotype, but persistent hypertension after surgery, recurrence and malignant behavior were all more frequently observed in patients with a noradrenergic tumor. Preoperative alpha-blocker treatment was given for 14 days or more in 29 patients (36%) and, although being more symptomatic at diagnosis, these patients had less often hemodynamic complications (10% vs. 24% in non-treated patients, p=0.05).

Conclusions: PCs are nowadays frequently diagnosed in asymptomatic patients, although most of these tumors still exhibit a secretory phenotype, which is adrenergic in 2/3 and noradrenergic in 1/3 of cases. The occurrence of hemodynamic complications during surgery is not significantly affected by this phenotype in our study, but noradrenergic tumors show a worst post-surgical outcome, with persistent hypertension and a higher rate of recurrence or malignant behavior. Our data also provide some support in favor of a prolonged (> 14 days) alpha-adrenergic blocker preoperative preparation, at least in patients with a secretory PC.

Growth in children prior to diagnosis of juvenile type 1 diabetes: A systematic review.

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Background: Juvenile onset type 1 diabetes (T1D) is one of the most common chronic diseases in childhood and shows a rising incidence over the past decades. The exact pathogenesis is still not completely understood, especially regarding possible environmental factors triggering disease onset.

Aim: We aimed to systematically review literature on growth in children prior to diagnosis of juvenile type 1 diabetes and to ascertain whether specific patterns of growth prior to diabetes onset, are a consistent phenomenon.

Methods: This systematic review was fulfilled according to the PRISMA Guidelines. In April 2020, three online databases were consulted (PubMed, Embase and Cochrane Library). Studies describing growth in children prior to juvenile type 1 diabetes onset and covering patient populations from birth till age at onset and not older than 20 years were assessed.

Results: 37 studies were included, involving 156,609 T1D cases. Of these, 5065 cases were matched with 462,772 healthy individuals and 1230 non-diabetic siblings. An increased weight gain, expressed as weight SDS from birth till diagnosis, in early childhood was found to be positively associated with the risk of T1D development. Moreover, we were able to ascertain a higher weight SDS in children at diagnosis. High BMI SDS at birth did not show any significant outcome.

Conclusion: There appears to be a clear association between the early environmental factor of accelerated weight gain in the first years of life, higher weight at diagnosis on one hand, and the risk for (later) juvenile onset type 1 diabetes, on the other.

Early effects of androgen deprivation on bone and mineral homeostasis in adult men: a prospective cohort study

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Objective: Long-term androgen deprivation therapy (ADT) negatively influences bone. The short-term effects on bone and mineral homeostasis are less known. Therefore, we aimed to investigate the early effects of ADT on calcium/phosphate homeostasis and bone turnover.

Design: Prospective cohort study

Methods: Eugonadal adult male sex offenders, who were referred for ADT to the endocrine outpatient clinic, received cyproterone acetate. Changes in blood markers of calcium/phosphate homeostasis and bone turnover between baseline and first follow-up visit were studied.

Results: Of 26 screened patients, 17 were included. The median age was 44 (range 20-75) years. The median time interval between baseline and first follow-up was 13 (6-27) weeks. Compared to baseline, an 81% decrease was observed for median total testosterone (to 3.4 nmol/L (0.4-12.2); P<0.0001) and free testosterone (to 0.06 nmol/L (0.01-0.18); P<0.0001). Median total estradiol decreased 71% (to 17.6 pmol/L (4.7-35.6); P<0.0001). Increased serum calcium (P<0.0001) and phosphate (P=0.0016) was observed, paralleled by decreased PTH (P=0.0156) and 1,25-dihydroxyvitamin D_3 (P=0.0134). The stable calcium isotope ratio ($\delta^{44/42}Ca$) decreased (P=0.0458), indicating net calcium loss from bone. Bone-specific alkaline phosphatase and osteocalcin decreased (P<0.0001 and P=0.0056, respectively), periostin tended to decrease (P=0.0500) whereas sclerostin increased (P<0.0001), indicating suppressed bone formation. Serum bone resorption markers (TRAP, CTX) were unaltered.

Conclusions: In adult men, calcium release from the skeleton occurs early following sex steroid deprivation, reflecting early bone resorption. The increase of sclerostin and reduction of bone formation markers, without changes in resorption markers, suggests a dominant negative effect on bone formation in the acute phase.

Biological variation and analytical goals of four thyroid function biomarkers in healthy European volunteers

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Background

Interpretation of thyroid function tests by means of biological variation (BV) data is essential to identify significant changes between serial measurements at an individual level. Latest BV data on thyroid parameters in adults included in the EFLM Biological Variation Database have been published in 2008.

Objectives

We aimed at determining the BV of four thyroid function test (thyroid-stimulating hormone (TSH), free thyroxin (FT4), free triiodothyronine (FT3) and thyroglobulin (Tg)) by applying recent recommendations to acquire BV data on a latest generation of immunoassay.

Methods

Nineteen healthy volunteers (8 males and 11 females) were drawn every week during 5 consecutive weeks. Samples were analyzed in duplicate on the Cobas 602 analyzer (Roche Diagnostics). After normality assessment, outlier exclusion, and homogeneity of variance analysis, analytical variation (CV_A), within-subject biological variation (CV_I) and between-subject biological variation (CV_G) were determined using nested ANOVA.

Results

CV_A, CV_I and CV_G were 0.9%, 19.7% and 37,6% for TSH; 3.6%, 4.6% and 10.8% for FT4; 2.2%, 6.0% and 8.6% for FT3; and 0.9%, 15.4% and 84.9% for Tg. Index of individuality (II) for all parameters was between 0.2 and 0.7. The reference change value was 54.7% for TSH, 16.2% for FT4, 17.7% for FT3 and 42.8% for Tg.

Conclusion

The integration of our updated and reliable BV characteristics for thyroid hormones can facilitate the interpretation of thyroid function tests by a better identification of significant change between serial measurements.

Central hypothyroidism: are patients undertreated?

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Objective: To investigate the dosage of thyroid hormone replacement in patients with central hypothyroidism (CHT) and to compare this with the dose in patients with primary hypothyroidism (PHT). The ETA guidelines suggest dosing should reach 1.2 – 1.6µg/kg body weight and aiming for free thyroxine levels (fT4) in the upper limit of normal. In addition, we explored and compared Quality of Life (QoL) between both groups, based on two questionnaires, the SF-36 health score and the thyroid specific ThyPRO score.

Methods: This is a monocentric, cross-sectional study, performed at the Ghent University Hospital (Belgium). We included 70 patients in total, 41 patients with CHT and 29 patients with PHT over a period of twelve months. At the moment of inclusion, all patients had to have a stable dose of levothyroxine over the past six months and patients with PHT needed to be euthyroid (defined as having a TSH level within the reference range, 0.2 – 4.5mU/L). All data was retrieved from medical files, questionnaires were self-administered.

Results: The CHT and PHT group were comparable regarding age and BMI. There was no statistically significant difference between both groups regarding total daily dose of levothyroxine (P=0.942), or dose levothyroxine per kg body weight (P=0.265). The mean total daily dose of levothyroxine (µg per day) was 100 [93.75 – 125.00] and 107.14 [81.25 – 132.14] in CHT and PHT, respectively. The mean dose levothyroxine per kg body weight was 1.34 [1.16 – 1.55] for patients with CHT and 1.51µg per day [1.14 – 1.73] for patients with PHT. Serum levels of fT4 and fT3 did also not differ between the two groups (P=0.269, P=0.132) and both fT4 and fT3 levels were in the normal (mid)range for the two groups. Regarding Quality of Life, we could not demonstrate any significant difference between both groups.

Conclusion: We could not demonstrate a difference in Quality of Life measures between patients with central and primary hypothyroidism. Although patients with CHT had a somewhat lower levothyroxine substitution dose than patients with PHT (total daily dose and dose levothyroxine per kg body weight), this difference was also not significant.

The role of insulin resistance and NAFLD in the cardiometabolic risk profile of type 1 diabetes

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Background and aims: People with type 1 diabetes (T1D) are increasingly suffering from overweight and at risk of developing insulin resistance (IR). IR may hamper glucose control and augment the risk of cardiovascular disease (CVD). Simultaneously, non-alcoholic fatty liver disease (NAFLD) is becoming increasingly prevalent in T1DM. The pathophysiology of NAFLD is linked to IR. The gold standard to assess IR is the euglycaemic clamp, an invasive and time-consuming test that cannot be performed in routine screening. The estimated glucose disposal rate (eGDR) can be used as an accurate, alternative estimation of IR. This study aims to determine the prevalence of NAFLD in T1D, to estimate IR using the eGDR and elucidate associations between NAFLD, IR and CVD.

Materials and methods: 296 T1D subjects were consecutively screened for NAFLD using ultrasound criteria and underwent anthropometry, clinical examination and laboratory testing. The eGDR was calculated as follows: eGDR (mg/kg/min) = 21,158 + (-0,09*waist circumference (cm)) + (-3,407*hypertension) + (-0,551*HbA1c (%)). A history of past CVD was determined by assessing the individual patient files. The eGDR was divided into 3 categories (<5.39; 5.39-7.75; >7.75 mg/kg/min), with the lowest category representing the highest degree of IR (Epstein et al., 2013).

Results: Median age was 48 years (range 18-88), median diabetes duration was 27 years (range 1-61), mean HbA1c: 7.6 ± 1.0%, mean BMI: 26.2 ± 4.5 kg/m^2. 36.1% of cases were overweight, 19.6% were obese. NAFLD was present in 20.6% of cases. Subjects with vs. without NAFLD were older (51 ± 16 vs 46 ± 16 y, p=0.013), had higher BMI (29.8 ± 5.0 vs 25.2 ± 3.9 kg/m^2, p<0.001), ALT (32 ± 21 vs 24 ± 11 U/l, p<0.001), γ-GT (38 ± 33 vs 28 ± 27 U/l, p=0.039), triglycerides (111 ± 86 vs 79 ± 39 mg/dl, p<0.001) and lower HDL-cholesterol levels (57 ± 15 vs 64 ± 17 mg/dl, p=0.001). Concerning IR, only 5.7% of subjects fell in the highest category, but 26.4% expressed mild IR. NAFLD prevalence was 41%, 40% and 12% in the high, medium and low IR groups respectively (p<0.001). eGDR was lower in NAFLD subjects (7.1 ± 2.0 vs 8.8 ± 1.6 mg/kg/min, p<0.001). Composite CVD was present in 8.8% (coronary artery disease (CAD) 5.8%, peripheral arterial disease (PAD) 4.7%, cerebrovascular accident (CVA) 1.4%). The prevalence of composite CVD (21.3 vs 5.5%, p<0.001), CAD (13.1 vs 3.9%, p=0.011), PAD (11.7 vs 2.7%, p=0.009) and CVA (4.9 vs 0.4%, p=0.029) were higher in the NAFLD group. The prevalence of composite CVD was 23.5%, 16.0% and 4.9% in the high, medium and low IR groups respectively (p=0.001). Independent risk factors for composite CVD were the presence of NAFLD (OR:3.96 [95%CI: 3.40-11.23], p=0.010), eGDR (OR:1.3, [95%CI: 1.00-1.80], p=0.047) and age (OR:1.1, [95%CI: 1.02-1.12], p=0.005) when including these parameters and BMI, gender and diabetes duration in the regression model.

Conclusion: NAFLD and IR are common in T1D and both are independently correlated with the presence of cardiovascular events, with the highest odds ratio for NAFLD. Although cross-sectional data do not prove causality, these results suggest a possible pivotal role for NAFLD and/or IR in the cardiometabolic risk profile of T1D. Longitudinal studies are needed to further investigate the role of NAFLD and/or IR as independent risk factors in T1DM.

The impact of antenatal depression on pregnancy outcomes in women with gestational diabetes mellitus and normal glucose tolerant women

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Aims: To determine the impact of antenatal depression on pregnancy outcomes in women with gestational diabetes mellitus (GDM) and women with normal glucose tolerance (NGT).

Methods: 1843 women from a Belgian multi-centric prospective cohort study (BEDIP-N Study) received universal screening for GDM with a 75g OGTT and the IADPSG criteria. The Center for Epidemiologic Studies - Depression (CES-D) questionnaire was completed at the time of the OGTT (before the diagnosis of GDM was communicated), and for women with GDM also in early postpartum. The SF-36 health survey was completed in early postpartum.

Results: GDM prevalence was 12.5% (231). Women with GDM were significantly more often depressed than NGT women [21.3% (48) vs. 15.1% (239), p=0.017] at the time of the OGTT. In the GDM subgroup, depressed women (n=48) had more often an ethnic minority background (EMB) [29.2% (14) vs. 15.4% (27), p=0.003], smoked more often during pregnancy [12.5% (6) vs. 4.0% (7), p=0.025], had a higher BMI in early pregnancy (27.9 ± 5.3 versus 26.3 ± 5.3 Kg/m², p=0.048), and attended less often the postpartum OGTT [68.7% (33) vs. 87.6% (155), p=0.002] compared to non-depressed GDM women (n=177). There were no significant differences in pregnancy outcomes between both groups. Depressed GDM women remained more often depressed postpartum [37.1% (13) vs. 12.4% (19), p<0.001] and had lower SF-36 scores than non-depressed GDM women. Compared to NGT women without depression (n=1342), depressed NGT women (n=239) had more often an EMB [18.8% (45) vs. 6.1% (81), p<0.001] , a lower education degree (p<0.001), less often a paid job [79.7% (189) vs. 94.0% (1258), p<0.001], smoked more often during pregnancy [5.4% (13) vs. 2.9% (39), p=0.044], had more often a first degree family history of diabetes [16.8% (39) vs. 11.2% (146), p=0.015], and had a higher BMI in early pregnancy (25.1 ± 4.7 vs. 24.2 ± 4.4 Kg/m², p=0.003). Rates of preeclampsia and labor inductions were significantly higher in the depressed NGT group compared to the NGT group without depression [resp. 3.3% (8) vs. 1.5% (20), p= 0.046 and 35.0% (75) vs. 27.4% (330), p=0.022]. After adjustment for confounders such as EMB, education,

smoking, BMI and glucose levels at the time of the OGTT, only the rate of labor inductions remained significantly increased [OR 1.40 (95% CI 1.01-1.93), p=0.041]. Depressed NGT women had lower SF-36 scores (p<0.001) postpartum compared to non-depressed NGT women.

Conclusions: Women who develop GDM have more often a depression before the diagnosis. GDM women with depression have similar pregnancy outcomes as GDM women without depression but are more often depressed postpartum with lower quality of life scores. NGT women with depression have similar pregnancy outcomes than NGT women without depression except for higher rates of labor inductions.

Clinical, biological and radiological characteristics of diabetic patients hospitalized for COVID-19 in a Belgian tertiary care center

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Introduction: In Belgium, 21.4% of patients hospitalized with COVID-19 are diabetic [1]. In this study, we describe the characteristics of diabetic patients hospitalized for COVID-19 in a Belgian tertiary care center.

Patients and Methods: The Clinics Ethics Committee approved the systematic registration of anonymized data from hospitalized patients with confirmed COVID-19 (N° CEHF 2020/22MAI/290), i.e. a positive SARS-CoV-2 PCR test on nasopharyngeal swab and/or computed tomography (CT) consistent with SARS-CoV-2 pneumonia in symptomatic patients. We retrospectively reviewed demographics, clinical, biological, and radiological data on admission from patients with known or newly-diagnosed diabetes. Survivors were compared to non-survivors to study prognostic factors of SARS-CoV-2 infection severity in diabetic patients.

Results: Fifty-six diabetic patients were identified among a total of 336 patients hospitalized with COVID-19 between March 11, 2020 and April 23, 2020, i.e. a 16.7% prevalence. Fifty-five had positive SARS-CoV-2 PCR (98.2%). Patient's characteristics are summarized in **Table 1**. None had type 1 diabetes. Most patients had comorbidities (93%), half of them having ≥ 3. The most frequently-used glucose-lowering and blood pressure-lowering agents were: metformin (71.5%), insulin (37.5%), sulfonylurea/glinides (25%), diuretics (44.5%), angiotensin-converting enzyme inhibitors (ACEI), and angiotensin II receptor blockers (ARBs) (64.5%). DDP4 inhibitors were used in 5.5% of patients. Fever (73%), cough (80%) and dyspnea (65.5%) were the commonest symptoms on admission. Treatment consisted of azithromycin (16.5%) and/or antibiotics (23%) and/or hydroxychloroquine (89%), and/or glucocorticoids (13%). Non-invasive ventilation was required in 18 patients (32%). Twelve patients (21.4%) were admitted to an ICU, 7 (58.0%) of them requiring invasive mechanical ventilation. The overall case-fatality rate was 17.9%, as 10 patients died from COVID-19. Compared to survivors, non-survivors were older (*p* 0.021), had more severe pneumonia on the basis of lung surface area involvement on CT (*p* 0.025), and lower cycle threshold (Ct) of PCR test (*p* 0.024), the latter used as a proxy for viral shedding. Non-survivors were also less often treated with metformin (*p* 0.024) but required more often antibiotics (*p* 0.041) for suspected or proven secondary lung infections (*p* 0.037). No statistically significant difference was found regarding ethnicity, HbA1c, diabetes duration, body mass index (BMI), chronic diabetes-related complications, COVID-19-related symptoms, biological values, and other therapies. Limitations of this study include its retrospective design, small population size, and missing data regarding diabetes duration and HbA1c.

Conclusion: In this monocentric cohort, we showed that diabetic patients hospitalized in Belgium for COVID-19 had mostly type 2 diabetes, and chronic hyperglycaemia-related complications. Moreover, half of them were obese. Age, but not BMI nor chronic glycaemic control, adversely influenced mortality. Although these findings are comparable to data from the multicentric CORONADO study [2], they need confirmation in larger series from other Belgian centers.

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Table 1. Clinical characteristics and COVID-19-related biological values and radiological data on admission according to vital outcome

Variables	Number of Patients with available data	All (N=56)	Survivors (N=45)	Non-survivors (N=10)	*p* value
Age (years)	**56**	66 ± 13	64 ± 12	74 ± 16	**0.021**
Female sex	**56**	26 (46.0)	22 (48.0)	4 (40.0)	0.737
BMI (kg/m²)	**55**	30.5 ± 6.0	30.0 ± 5.0	31.0 ± 8.0	0.633
Stratification of BMI	**55**				0.101
< 25 kg/m²		9/55 (16.5)	6/46 (13.0)	3/9 (33.0)	
25-29 kg/m²		17/55 (31.0)	16/46 (35.0)	1/9 (11.0)	
30-34 kg/m²		19/55 (34.5)	16/46 (35.0)	3/9 (33.0)	
35-39 kg/m²		6/55 (11.0)	6/46 (13.0)	0/9 (0.0)	
≥ 40 kg/m²		4/55 (7.0)	2/46 (4.0)	2/9 (22.0)	
Diabetes type	**56**				0.551
Type 2		51/56 (91.0)	41/46 (89.0)	10/10 (100.0)	
Secondary		3/56 (5.5)	3/46 (6.5)	0/10 (0.0)	
Newly-diagnosed [a]		2/56 (3.5)	2/46 (4.5)	0/10 (0.0)	
Diabetes Duration (years)	**49**	9 [0-30]	9 [0-30]	9 [0-16]	0.743
HbA1c (%)	**46**	7.0 [4.1-11.7]	7.0 [5.4-11.7]	6.7 [4.1-9.4]	0.368
Dyslipidemia	**56**	43/56 (77.0)	34/46 (74.0)	9/10 (90.0)	0.424
Current Smoking	**52**	2/52 (4.0)	1/43 (2.5)	1/9 (11.0)	0.319
Chronic glucose -related vascular complications[b]	**54**	30/54 (55.5)	25/46 (54.5)	5/8 (62.5)	0.720
Ground glass opacities/crazy paving	**45**	44/45 (98.0)	37/38 (97.5)	7/7 (100.0)	1.000
Chest Imaging severity	**41**				**0.025**
Mild to moderate (<25%)		20/41 (49.0)	20/35 (57.0)	0/6 (0.0)	

Extensive (25-50%)		16/41 (39.0)	12/35 (34.5)	4/6 (67.0)	
Severe to critical (>50%)		5/41 (12.0)	3/35 (8.5)	2/6 (33.0)	
Ct SARS-CoV-2 RT-PCR[c]	**53**	31 [18-39]	32 [19-39]	23 [18-38]	**0.024**
Laboratory values [d]					
Plasma glucose (mg/dl)	**54**	167 [37-349]	181 [37-349]	133 [87-288]	0.266
C-reactive protein (mg/l)	**56**	74 [2-413]	74 [2-413]	85 [18-263]	0.881
GFR (ml/min/1.73m²)[e]	**55**	68 [12-110]	71 [16-110]	58 [12-104]	0.647
Lymphocytes (10³/mm³)	**56**	0.9 [0.1-3.1]	0.9 [0.1-2.1]	0.9 [0.7-3.1]	0.369
Neutrophils/lymphocytes ratio	**56**	5.2 [0.7-25.3]	5.5 [0.7-25.3]	3.0 [1.2-17.9]	0.164
Eosinophils (10³/mm³)	**56**	0.0 [0.0-0.9]	0.0 [0.0-0.9]	0.0 [0.0-0.1]	0.346

Data are expressed as means (± SD), medians [min-max], and numbers (%). Differences between groups were assessed by Student's t-Test/Mann-Whitney U Test, or Chi-Square test/Fischer's exact test according to distribution.

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin A1c; Ct, cycle threshold, GFR, glomerular filtration rate

a HbA1c ≥6.5% on admission

b Included retinopathy, nephropathy, neuropathy, foot ulcer, ischemic heart disease, stroke/transient ischemic attack, peripheral arterial disease

c RS-CoV-2 RNA in nasopharyngeal swabs was detected using COVID-19 genesig® RT-PCR assay (Primerdesign Ltd, Chandler's Ford, United Kingdom) in a LightCycler 480 instrument (Roche Diagnostics, Mannheim, Germany). Probes and primers target RNA-dependent RNA polymerase (RdRp) gene. A cycle threshold < 40 was considered positive.

[d] Also included platelet count, lactate dehydrogenase (LDH), creatine kinase (CK), aspartate-aminotransferase (AST), alanine-aminotransferase (ALT); non-significant, $p > 0.05$.

[e] Calculated with CKD-EPI formula.

Soft drink intake on time of hypoglycaemia during insulin tolerance test: Effects on pituitary response and comfort for the patient

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Background and aim*:* Insulin tolerance test (ITT) is the gold standard for the diagnosis of cortisol and growth hormone deficiencies in adults. Once hypoglycaemia (< 40 mg/dl) is achieved, some medical centers give sugar to their patients (food, drink or glucose infusion), others do not and let the blood glucose rise spontaneously. Although critical hypoglycaemia results in discomfort and potential complications for the patients there is so far no recommendation on the subject. The aim of our study was to compare the stress response induced by insulin hypoglycaemia in healthy subjects, depending on whether or not they received a sugar-sweetened beverage on time of hypoglycaemia.

Method: We conducted a prospective, single-center study that recruited 10 healthy subjects (5 women and 5 men; mean age of 28.5 years 6.67 SD). Each subject performed two ITT: during one they received 150 ml of regular Coca-Cola and during the other they received 150 ml of diet Coca-Cola (zero) after hypoglycaemia was achieved. In addition to usual hormone measurements we performed glucose continuous monitoring analysis and salivary cortisol and cortisone dosages.

Results: Regular cola significantly shortened the time spent in severe hypoglycaemia (<40 mg/dl) (10 min vs 25 min; p = 0.03). The median duration of side effects tended also to be shortened (45' versus 100'; p = 0.47) and the subjects discomfort was significantly reduced as evaluated by a visual analog scale (VAS score 2 vs 3.4; p = 0.04). Although the median peak concentration of plasma cortisol was significantly higher in the absence of sugar-sweetened beverage (579 vs 526 nmol/l), we didn't observe any significant difference in terms of plasma cortisol increment, median peak concentration of salivary cortisol and cortisone, and of serum GH and ACTH. Moreover all subjects demonstrated adequate stimulated cortisol and GH levels (cortisol > 374 nmol/l with a minimum of 390 nmol/l; and GH > 3 µg/l). The best correlation between plasma cortisol and salivary cortisol as well as cortisone levels was obtained at time 120' (salivary cortisol r = 0.90, salivary cortisone r = 0.92; p <0.001).

Conclusion: Our study suggests that glucose intake after achieving hypoglycaemia during ITT decreases the duration of severe hypoglycaemia and improves patient's comfort while ensuring adequate pituitary response according to the most recent thresholds proposed in the literature. Our results also confirmed the necessity to revise the stimulated plasma cortisol thresholds downwards, and the interest and validity of salivary cortisol and cortisone measurements.

Changes in adipocytokines and myokine expression during weight loss in subjects with obesity

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Background and aim: Adipose and muscle tissue dysfunction are associated with obesity-related complications, especially insulin resistance (IR) and inflammation, which improve after weight loss. The underlying mechanisms are however not yet fully understood. This study investigates changes in systemic and regional markers of IR and inflammation during weight loss in subjects with obesity.

Materials and methods: Twenty subjects with obesity (age 49±10years, 14 men) were recruited prior to gastric bypass surgery. On baseline, and six months and one year thereafter, subcutaneous abdominal adipose tissue (SAT), skeletal muscle and fasting serum samples were collected. Sixteen subjects had biopsies in follow-up. Serum levels of C-reactive protein (CRP), glucose and insulin were determined using standard laboratory assays and interleukin-6 (IL-6), interleukin-10 (IL-10) and tumor necrosis factor alpha (TNF-α) using ELISA. HOMA-IR was calculated. mRNA expression in adipose and muscle tissue of glucose transporter 4 (GLUT4), bone morphogenetic protein 4 (BMP4), IL6, IL10, monocyte chemoattractant protein 1 (MCP1), insulin receptor substrate 1 (IRS1) and TNFα was determined using qPCR.

Results: During weight loss, BMI decreased along with systemic improvement in inflammation (CRP and IL-6 levels) and IR (see table). Serum IL-10 and TNF-α levels did not change ($p>0.05$). In muscle tissue, mRNA expression of BMP4, GLUT4 and IL-6 decreased and MCP1 and IRS1 increased. In SAT, mRNA expression of BMP4, IL-6, IL-10 and MCP1 decreased and GLUT4 increased (see table). IL-10 expression, only in muscle tissue, and TNF-α expression, in both tissues, remained unchanged (all $p>0.05$).

	Baseline		6 months	1 year
BMI (kg/m²)	43.6±4.7		**32.3±4.2****	**29.8±3.5****
Serum CRP (nmol/)	41.9	(21.9-80.95)	**14.29 (8.57-26.67)****	**8.57 (8.57-19.05)****
HOMA-IR	6.41	(4.64-7.62)	**(0.84-1.42)****	**0.92 (0.72-1.39)****
Serum IL6 (pg/ml)	2.70	(2.29-4.51)	(1.73-4.39)	**1.43 (1.09-2.60)***
Muscle BMP4°	12.0	(8.8-14.3)	**7.7 (6.7-8.4)***	**9.6 (6.6-11.0)***
Muscle GLUT4°	833.1	(740.6-957.9)	**676.6 (653.6-718.6)***	860.2 (735.7-909.9)
Muscle IL6°	1.5 (0.9-2.4)		**0.4 (0.3-0.5)****	**0.3 (0.2-0.4)****
Muscle MCP1°	3.3 (2.4-4.9)		**7.2 (6.3-9.4)****	**10.1 (8.9-12.1)****
Muscle IRS1°	155.2	(125.6-233.7)	**215.6 (167.0-272.0)***	**198.3 (193.3-274.3)***
SAT BMP4°	246.8	(200.6-338.5)	**147.5 (127.4-216.3)***	188.8 (167.2-205.1)
SAT GLUT4°	4443 (3915-5578)		**5876 (5078-7018)****	**5405 (5000-6296)***
SAT IL6°	2953 (1580-4531)		**(31.8-85.4)****	**56.1 (31.6-72.1)****
SAT IL10°	200.6	(95.8-276.2)	**(49.4-129.0)***	**35.2 (32.0-64.8)****
SAT MCP1°	6069 (3052-8433)		**1519 (1082-2203)***	**1172 (1057-1310)***

Data presented as median (25%-75%). °mRNA expression expressed as fold change with reference to household genes ($x10^{-3}$). Bold numbers indicate significant differences from baseline (*p<0.05 and **p<0.001).

Conclusion: Systemic improvements in inflammation and IR after GBS are mirrored by changes in tissue expression of inflammatory adipocytokines and myokines during weight loss in a population with obesity. Further research needs to clarify whether addressing these inflammatory pathways in obesity might help prevent or mitigate obesity-related complications.

CLINICAL CASE REPORTS

Diabetic muscle infarction

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Case: A 77-year-old woman, with a 50-year history of type 2 diabetes mellitus and multiple micro- and macrovascular complications, was hospitalized for a foot ulcer on a chronic Charcot foot. On admission, systematic anamnesis revealed back pain around L1-L2 for a week. There was no history of trauma or fever. Examination was normal except a symetrical loss of sensitivity on the feet related to his diabetic polyneuropathy. On admission, blood test showed an inflammatory syndrome with elevated C-reactive protein (CRP) at 191.3 mg/L (N < 5 mg/L), leukocytosis at 13.770 10^3/L and rhabdomyolyses with creatinine kinase (CK) at 8027 U/L (N: 20-180 U/L). The glycosylated hemoglobin was in the target at 6.1%. Coronarography revealed a short minor stenosis on the anterior intraventricular artery. Magnetic resonance imaging (MRI) of the spine revealed an herniated disc and, incidentally, an increased signal intensity on T2 of the right gluteal muscle. To exclude myositis associated with connective tissue disease and infectious myopathies, we had searched antinuclear antibodies, antineutrophil cytoplasmic antibodies and done blood cultures who were negative. A muscle biopsy showed a necrotic and inflamed muscle. Finally, a PET-CT looking for other muscle lesions highlighted an onset of necrosis in the left gluteal muscle. The diagnosis of bilateral and asymptomatic diabetic muscle infarction was made. The treatment consisted of analgesia, aspirin and bed rest. The control after three months was favorable with a normalization of the blood test and a regression of the T2 hypersignal and the peripheral enhancement of the gluteal muscles. She underwent surgery for the hernia.

Discussion: Diabetic muscle infarction also referred as spontaneous diabetic myonecrosis is a rare but well-recognized complication of longstanding and poorly controlled diabetes mellitus with microvascular complications. First reported in 1965, less than 200 cases reports were published in the literature. Diabetic muscle infarction is more common in women and occurs in both type 1 and 2 diabetes mellitus. The mean age of onset is 44,6 years. The pathogenesis of this muscle lesion remains unclear but seems related to atherosclerosis, diabetic microangiopathy, vasculitis with thrombosis and ischemia-reperfusion injury. The typical clinical presentation includes acute pain in the affected muscle and local swelling. Diabetic muscle infarction occurs most often in the thigh muscles but other locations were reported. Bilateral affection occurs in less than 33% of cases. Biological findings are nonspecific such as elevated CK, CRP and leukocytes. MRI with intravenous contrast enhancement is the most useful diagnostic technique that shows an increased signal of the affected muscle in T2-weighted. Muscle biopsy can provide a definitive diagnosis by showing muscle necrosis and oedema as well as occlusion of arterioles and capillaries by fibrin but it is generally not recommended because it delays the recovery and is associated with recurrences. The treatment is conservative and includes rest, low-dose acetylsalicylic acid, analgesia and optimal glycemic control. The mean duration of symptoms is about 4 weeks. Recurrence rates exceeds 40% and usually involves different muscles.

Conclusion: We report a case of bilateral and asymptomatic diabetic muscle infarction as an unusual cause of elevated CK in a patient with long-stading diabetes mellitus.

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A shining heart at Valentine's Day

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Introduction

Primary adrenal lymphoma is rare, representing less than 1% of non-Hodgkin lymphomas.[1] The clinical presentation is non-specific, symptoms of adrenal insufficiency may occur with bilateral lesions, and work up can be tricky.2

Background

A 60-year-old man was admitted mid-January 2020 for acute left abdominal pain. He had no medical history and didn't smoke or take any medication. He had no history of recent trauma. Abdominal CT-scan showed a voluminous (61x57x47mm), heterogeneous, hemorrhagic mass in left adrenal gland with a high spontaneous density (45UH). Pheochromocytoma diagnosis was first suspected although 24-hours urine fractionated metanephrines and catecholamines measurements were only slightly increased (NA:1.1xULN and NMN:1.2xULN). Hormonal evaluation did not demonstrate excessive cortisol or sexual steroids secretion. 18F-FDG PET-CT imaging revealed intense FDG-uptake in both adrenal glands, heart and liver. With this new information, the differential diagnosis includes carcinoid cardiac tumor, malignant cardiac myxoma, lymphoma, sarcoma and metastases. Tumor markers (5HIAA, NSE, CA 19-9, CA 125, CEA, PSA, β-hCG) were negative. For Valentine's Day, cardiac MRI confirmed a pathological thickening of right inter-atrioventricular groove with marked late enhancement at this level, corresponding to pathological areas in isotopic imaging. On the other hand, MRI did not show any lesion in the liver. Next day, patient presented acute right flank pain similar to the one he had on left side one month earlier. New abdominal CT-scan showed a large hemorrhage in right adrenal gland that was not present on 18F-FDG PET-CT performed 3 days before. Latest Ga-DOTATATE-PET imaging didn't show anywhere STT-receptors presence. Morning cortisol level (411 nmol/L) remained non-suggestive of adrenal insufficiency. A research of antiphospholipid syndrome was also negative. The patient never had any sign of infection. This case was discussed by web-conference with the French experts of the national COMETE multidisciplinary committee. It was decided to obtain histology from left adrenal tumor by percutaneous biopsy, which was performed in a specialized center, using a coaxial 16G needle with post-biopsy gelatin injection, and 24H post-biopsy monitoring. This was preferred to adrenalectomy because the radicality of surgery might have changed depending on histological diagnosis. Unfortunately two CT-guided biopsies did not succeed to obtain enough material for required-immunostaining to characterize a suspected T lymphoma. Right adrenalectomy was finally performed and a postoperative hydrocortisone supplementation was prescribed. Histological analysis showed a high grade non-germinal center B-cell like lymphoma with BCL6 rearrangement. The patient started an R-CHOP protocol, reaching a complete metabolic response within three cures.

However the patient presented a primary adrenal insufficiency after the right adrenalectomy, which still requires hydrocortisone supplementation.

Discussion

Adrenal incidentaloma exists in roughly 6% of the population.[3] While unilateral incidentaloma are usually benign, bilateral incidentaloma (15% of total incidentaloma[3]) are more likely to be malignant or functional.[3]

In a 2002 retrospective review, among 85 patients with an adrenal incidentaloma requiring pathological diagnosis, only one was found with adrenal lymphoma, which presented as a bilateral incidentaloma.[4]

In a recent retrospective study, bilateral adrenal lesions were found in up to 71% of adrenal lymphoma and were more likely to be associated with adrenal insufficiency, supposedly because of lymphomatous infiltration[1]. Therefore it is recommended to look for adrenal insufficiency in all patient with bilateral adrenal lesions.[1]

Our patient presented adrenal hemorrhage and myocardium involvement, which are rarely present with adrenal lymphoma.[1] FDG-PET is decisive for revealing extra-adrenal locations, even if CT or MRI is negative.[1]

Conclusion

This case underlines importance of complementary investigations in all patients with bilateral adrenal lesions, especially to rule out adrenal insufficiency. It also underlines importance of discussing complex cases or atypical presentations with experts as allowed by COMETE or ENDO-ERN networks.

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The importance of including post-operative thyroglobulin levels in the decision-making process towards adjuvant radioiodine treatment in patients with papillary thyroid cancer.

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The treatment of papillary thyroid cancer consist of surgery and if indicated post-surgical administration of radioiodine with the initiation of thyroid hormone substitution. Whether or not a patient receives a post-operative radioiodine treatment largely depends on the pathological staging (TNM).

Through observational data, the benefit of additional radioiodine treatment was only significant in patients with thyroid cancer classified as high risk according to the characteristics described by the American thyroid association (pT4, proven metastatic disease). In ATA low risk patients (T1a) post-operative radioiodine treatment is not suggested as there is no evidence suggesting the iodine treatment effects the long term outcome. In ATA low risk patients (T1b, T2) and ATA intermediate risk patients (T3 – tumor size > 4cm) radioiodine therapy may be considered if other adverse characteristics are present, for example an aggressive histology. In ATA intermediate risk patients (T3 with microscopic extrathyroidal extension, T1-3 N1a, T1-3 N1b) radioiodine treatment is generally favoured due to the higher risk of persistent or recurrent disease.

Case 1: A 33-year old female patient diagnosed with a follicular variant of papillary thyroid cancer underwent a total thyroidectomy in 2017. The postoperative staging consisted of a pT1b lesion of 2.4 cm limited to the thyroid gland for which postsurgical iodine treatment is not routinely recommended. Through multidisciplinary consultation, it was decided to treat the patient with 30 mCi radioiodine as the thyroglobulin was 0.75 ng/mL four months post-operative. The post therapy total body 131I scintigraphy with SPECT-CT showed several foci of costovertebral and pelvine iodine uptake without CT-graphic nor MRI correlates. It was decided to conceive these hotspots as micro-metastases, indicating the need of an additional treatment with 100 mCi radioiodine. Post therapy there were no clinical, biochemical (undetectable thyroglobulin) and scintigrafic residual tumor foci.

Case 2: A 37-year old female patient was diagnosed with a follicular variant of papillary thyroid cancer after a right robot-assisted hemithyroidectomy. The patient underwent a completion thyroidectomy in 2019. Pathological examination showed a lesion of 7 cm limited to the thyroid gland, indicating a pT3 staging. For this type of lesion the American thyroid association guidelines indicate to consider additional radio-iodine therapy if other adverse features are present. In this case there were none. Nevertheless the decision was made to give the patient an adjuvant treatment with 100 mCi radioiodine since the thyroglobulin level two months post-operative was 0.80 ng/mL. Post therapy scan showed two foci of pelvine iodine uptakes. CT showed no corresponding lesions. MRI showed a small focus of sclerosis left supra-acetabular with minimal surrounding bone oedema (17 mm). A targeted biopsy was not possible, but

morphologically the lesion was highly compatible with a bone metastasis. Six months after radioiodine therapy thyroglobulin is undetectable. Morphologic follow up is planned.

By following the guidelines based on the pathological staging, both patients do not have a formal indication for radioiodine treatment. These cases illustrate the importance of including the post-operative thyroglobulin level in the decision-making process whether or not to administer post-surgical radioiodine treatment. The nadir of postoperative serum thyroglobulin level is usually reached 4 weeks postoperatively. Observational data have shown that a thyroglobulin level around 0.2 ng/mL has the best sensitivity and specificity for detecting persistent disease. In conclusion: combining TNM staging and post-operative thyroglobulin allows for selective radioiodine use as well as for detection of unexpected metastatic disease.

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Carney complex presenting with significant cardiac myxomas and acromegaly, a case-report.

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Case:

An eighteen-year-old male was forwarded to our department by the ophthalmologist because of the resection of an angiomyxoma of the right eyelid. Medical history included multiple surgically excisions of myxomatous tumors from the skin (gluteal, scapular…). Clinical examination showed some lentiginous lesions on his back and more important clear stigmata of acromegaly (tall stature, wide nose, large hands…). Hence our suspicion of a syndromic disorder, in particular the Carney Complex, a quick referral to the cardiologist was ordered. TTE showed three prominent cardiac lesions in both ventricles near the tricuspid and mitral valve. TEE and CT angiography confirmed the lesions, no significant valve insufficiency or stenosis was observed. However due of the high risk for systemic embolization and risk of cardiac outflow tract obstruction and subsequently heart failure, our patient was admitted for semi-urgent cardiac surgery. Hormonal evaluation confirmed the diagnosis of acromegaly with significant elevation of growth hormone levels (GH 30,93 mcg/L and IGF-1 1472 ng/mL). Subsequently magnetic resonance imaging (MRI) of the brain displayed two small pituitary adenomas (fig. 1). Lanreotide (120 mg), Somatuline depot injection, every 4 weeks was started prior to the cardiac surgery, in treatment of acromegaly and for prevention of intra/postoperative pituitary apoplexy. The evidence for the timing of cardiac surgery when a macro-adenoma had been present is at least controversial. Some reports recommend to consider trans-sphenoidal resection of the adenoma first or do an ‘off pump’ cardiac surgery given the high prevalence of life-threatening pituitary apoplexy postoperatively (1). Our patient underwent a successful surgical resection of four cardiac myxomas via median sternotomy (fig. 2).

Besides a rigorous search for other major criteria was performed. Scrotal echography showed two small lesions congruent with large cell calcifying sertoli cell tumors (LCCSCT). Because of the presence of three major criteria, a search for the identification of a pathogenic variant in the PRKAR1A gene was started. The Carney complex (CNC) is a rare autosomal dominant syndrome which is characterized by multiple myxomatous tumors, including cardiac myxomas, pigmented lesions of the mucosae and skin and numerous endocrine and non-endocrine neoplasms (2). The syndrome is generally caused by inactivating mutations in the PRKARA1 gene which codes for an important regulatory subunit for protein kinase A and subsequently leads to excessive cell proliferation (3). We refer to a recent review, which summarize important criteria for the diagnosis. Genetic counseling is recommended if a patient has two or more diagnostic criteria. If present, it’s recommended for testing other family members as well because there are multiple manifestations of the disease that require (urgent) treatment (4). Genetics showed eventually the presence of

c.549+1G>A variant on exon 6 located on the PRKAR1A gene and very likely confirms the diagnosis of Carney complex.

In conclusion, the Carney complex is a rare autosomal inherited syndrome with potential life-threatening manifestations. If the syndrome is suspected, semi-urgent echocardiography has to be performed to detect cardiac myxomas. If present early cardiac surgery is recommended hence the risk of fatal cardiovascular events in this especially young population of patients. However, measurements have to be taken to detect and prevent intra/postoperative pituitary apoplexy given the high prevalence of adenomas.

Figures:

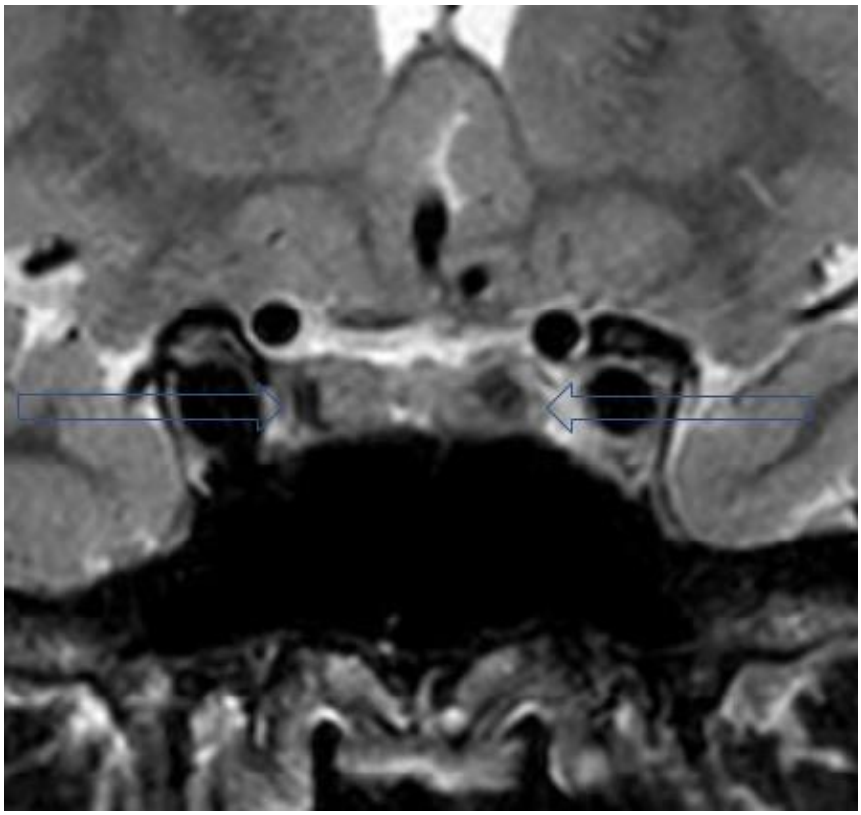

Figure 1: Pituitary MRI (coronal plane) shows 2 (small) pituitary adenomas (respectively 7-7,7 mm and 5 mm).

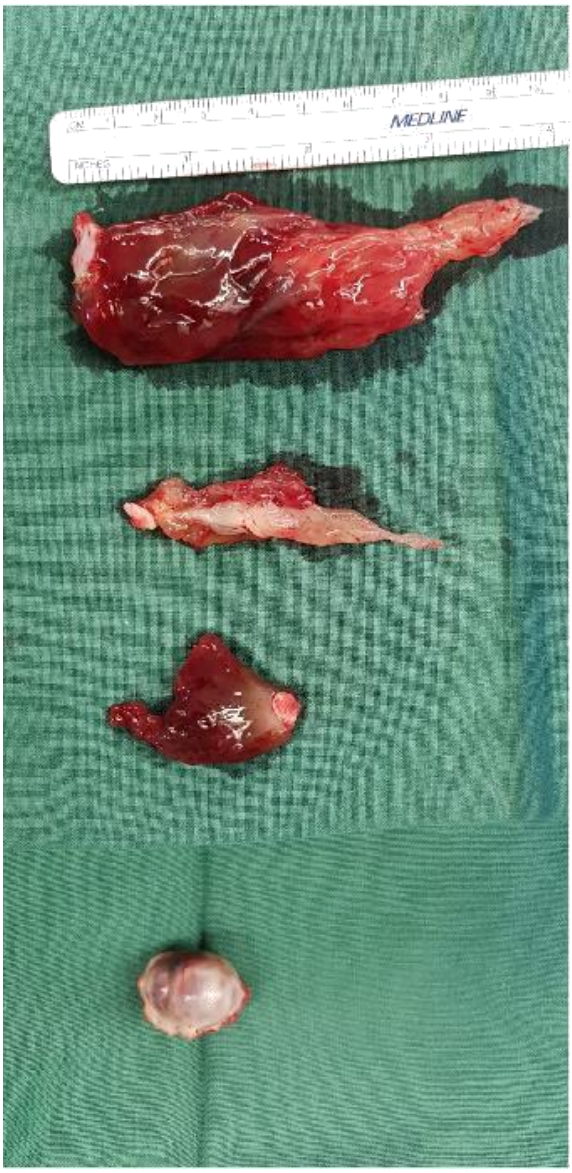

Figure 2: Successful surgical resection via median sternotomy of four cardiac myxomas (one myxoma in right ventricle and three myxomas in left atrium/ventricle).

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Fertility in men with 5-alpha reductase deficiency

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Introduction

5 Alpha reductase deficiency (5-ARD) is a rare autosomal recessive disorder causing disturbance of sex development. 5 Alpha reductase is an enzyme involved in steroid metabolism, catalyzing testosterone into dihydrotestosterone (DHT), its potent form. 5-ARD therefore results in lower DHT and higher testosterone values. DHT is crucial for the differentiation of the urogenital sinus and genital tubercle into the external genitalia, urethra and prostate, while the vas deferens and seminal vesicles are testosterone dependent. [1]

Different virilization problems have been reported in 5-ARD patients, including clitoral-like phalluses, bifid scrotums, hypospadias, vaginal pouches and underdeveloped prostates. [1-3] Puberty and masculinization of the brain are largely testosterone (rather than DHT) dependent. At puberty these patients will therefore have increasing muscle mass and deepening of their voices. Hence, it is of great importance to perform a correct gender assignment at birth. [1, 2]

Besides impaired virilization, subfertility is common. Varying causes have been reported including cryptorchidism and abnormal prostate development with low semen volumes and impaired seminal liquefaction, which is mediated by PSA. [1, 2] Fertility treatments depend on the grade of impaired spermatogenesis and seminal transport. For men with normal sperm concentration and motility, spontaneous or intrauterine insemination is possible. In vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) has been proven successful in men with small and viscous semen samples. [2, 4]

In this case we will highlight the importance of fertility in 5-ARD patients, as well as suggest a possible diagnostic work up and further management.

Case presentation

A man in his mid-twenties presented to our outpatient clinic with a known 5-ARD since birth. He was in good health, yet presented with osteopenia. This suggests DHT to be important in bone development. He was born with a bifid scrotum, underdeveloped penis and penoscrotal hypospadias for which he received hormonal treatment and surgical correction. Afterward, no further interventions were needed and his pubertal development was normal.

He now presented with a fertility wish since 3 months. Sexual intercourse and ejaculation are possible, yet the ejection phase is impaired, with a need for manual urethral semen evacuation.

A diagnostic work up was undertaken, including blood tests, prostatic imaging, semen analysis and genetic testing. On blood tests, low DHT levels were confirmed, however with normal testosterone, LH, FSH, prolactin, estradiol and inhibin B. The latter is reflective of the Sertoli cell functioning, and therefore suggests spermatogenesis to be intact.

On prostatic ultrasound, seminal vesicles and vas deferens were normally developed. The prostate however was hypoplastic with a measured volume of only 5 grams, 4 times smaller than expected yet normal for 5-ARD patients. [2, 3] Figure 1

0.3 ml of viscous, highly concentrated semen was retrieved for analysis, comparable to previous reports in 5-ARD patients.[2] Initial motility was impaired, however, after capacitation testing, 1/3rd of sperm cells progressed, with a total motility count of 30 million cells.

Given the low volume of viscous semen but sufficient total motile count of the sperm cells after capacitation, IVF was considered suitable.

Conclusion

This case reminds us of the fertility problems associated with 5-ARD. Clinicians should be aware of the options, ranging from spontaneous/ intrauterine insemination to ICSI. Proper management of these patients is multidisciplinary, starting at birth.

Written Informed consent was given by the patient for the publication of his case and the associated images.

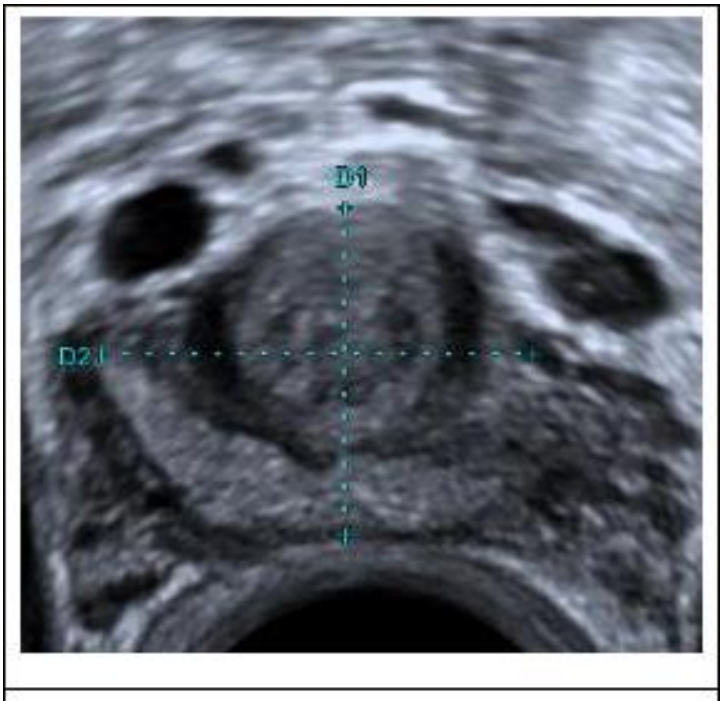

Figure 1: Hypoplastic prostate with volume of 5 gram

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(Non-FDG) functional imaging thyroid incidentaloma

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Background

Thyroid incidentaloma are asymptomatic thyroid nodules that are discovered on an imaging study performed to evaluate other structures. Clinically unrecognized thyroid nodules are common and can be found in up to 50–60% of patients at autopsy.[1] Increased use of imaging modalities of better quality in the modern era has resulted in an increased detection of incidental thyroid nodules. The prevalence rate is 67% with ultrasonography (US) imaging, 15% with computed tomography (CT) or magnetic resonance imaging (MRI) of the neck, and 1-2% with fluorodeoxyglucose (FDG) positron emission tomography.[2] Their clinical importance is primarily related to the need to exclude thyroid cancer. In this study we report on thyroid incidentaloma found on non-FDG functional imaging.

Clinical cases

1 A 70-year old man was referred for hypercalcemia and nefrolithiasis. He was diagnosed with primary hyperparathyroidism. As ultrasound and scintigraphy could not detect a localization, ***18F-fluorocholine PET/CT*** was performed. It showed 2 spots of uptake, one measuring 16 mm below the right thyroid lobe and another one inside the right thyroid lobe. The latter corresponded to a 9 mm hypoechogenic intrathyroidal nodule on ultrasound. The patient underwent right hemithyroidectomy and parathyroid exploration. Anatomopathological examination revealed a parathyroid adenoma and a papillary thyroid carcinoma, which had been removed completely.

2 A 76-year old man was referred for a thyroid incidentaloma on a ***68Ga-DOTATATE PET/CT.*** The scan was performed for diagnosis of a pancreatic neuroendocrine tumor (NET) and revealed a spot of high somatostatine receptor (SSTR) expression in the left thyroid lobe, in a hypoechogenic 2.5cm nodule on ultrasound. Fine-needle aspiration cytology (FNAC) of this nodule showed a Bethesda VI result. After recovery from a Whipple procedure, the patiënt underwent a total thyroidectomy. Pathology showed a 24 mm papillary thyroid carcinoma with largely follicular growth pattern, which had been removed completely. Postoperative thyroglobuline was low (1,37 ng/ml). The patient received 30 mCi radioiodine, with no distant uptake at the post-therapy scan.

3 A 65-year old man was diagnosed at our Department of Endocrinology for a papillary thyroid carcinoma (T3r1N0) in 2016. He underwent total thyroidectomy, followed by radioiodine therapy (100 mCi). One year later the stimulated thyroglobuline was below the detection limit and there was no uptake at the iodine-123 scan. In 2018 he was

diagnosed with a bilateral cervical lymph node recurrence for which he underwent surgery followed again by 100 mCi radioiodine. There was no uptake at the post-therapy scan. The patient also had a history of prostate adenocarcinoma in 2008. In his urologic follow up a ***68Ga-PSMA PET/CT*** was performed in 2019, and showed 2 spots of Prostate Specific Membrane Antigen (PSMA) accumulation in cervical lymph nodes. Ultrasound, FNAC and eventually surgical reintervention confirmed local recurrence of papillary thyroid carcinoma, which did not take up radioiodine. Adjuvant external radiation therapy was applied.

4 A 42-year old man was referred for a hotspot in the isthmus of the thyroid observed on a ***99mTc-diphosponate scintigraphy***. This bone scan had been performed for mid-thoracic back pain and was negative for bone metastasis. Ultrasound evaluation showed a normal homogenous thyroid.

Conclusion

1 We report four cases of thyroid incidentaloma on (no-FDG) functional imaging modalities. Not all but some may be malignant. All patients with a thyroid incidentaloma, independent of the mode of detection, need a dedicated neck US with risk stratification, followed by fine needle aspiration if necessary.

2 Apart from FDG-PET, Choline, Somatostatin receptor (SSTR) and Prostate Specific Membrane Antigen (PSMA) imaging are other molecular nuclear techniques which can potentially identify radioiodine-refractory differentiated thyroid cancer (RAIR-DTC).[3]

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A rare ABCC8 gene mutation causing severe Maturity-Onset Diabetes of the Young (MODY-12): case report and mini review

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Context: Maturity-Onset Diabetes of the Young (MODY) refers to a group of monogenic β cell disorders (1). MODY12 comprises various mutations in the ATP-binding cassette transporter subfamily C member 8 (ABCC8) gene of the ATP-sensitive potassium (K-) channel and is a condition that is not frequently encountered, comprising 1% of all MODY types (1). Gain-of-function ABCC8 mutations can result in neonatal diabetes mellitus and/or MODY12, whereas loss-of-function mutations can cause neonatal hyperinsulinism and hypoglycemia (1). Moreover, the possibility of an overlap and development of MODY12 in patients with congenital hyperinsulinism has been reported (1).

Case description and evidence acquisition: Here we present a case of a 35-year old woman with a severe disease course (with all diabetic microvascular complications and presentation with a Charcot arthropathy) and a rare mutation in the ABCC8 gene. We provide a review of all published cases of
MODY12 between 2018 and June 15th 2020 by conducting a structured search for “ABCC8”, “Maturity-Onset Diabetes of the Young”, “MODY”, “MODY12” and “Charcot” on Pubmed and including relevant case reports, case series and genetic articles describing case outcomes.

Evidence synthesis: We included 54 subjects with 39 different ABCC8 mutations. To the best of our knowledge, the c.3544C>T p.(Arg1182Trp) variant seen in our patient, has only been reported once before in 2014 in a patient having neonatal diabetes mellitus (2). MODY12 includes a heterogeneous spectrum of diseases with age at onset varying between a few weeks - 42 year old, HbA1c at diagnosis ranging between 5.6 - 13.7% (38 mmol/mol - 126 mmol/mol). Complications have often not been reported in MODY12 cases, but – when documented – the clinical heterogeneity (phenotype and complication rate) appeared large, in part explained by the type and location of the mutation (3).

However, different phenotypes can be seen within relatives with the same mutation, as documented in several cases (3) and also illustrated by our case. To the best of our knowledge up till now no Charcot arthropathy has been described in MODY12. Overall, in 17% of subjects a sulphonylureum (SU) was started after genetic diagnosis. In 15% of subjects this led to a cessation of insulin; in one other case the dose of insulin could be reduced. Evidence suggests that in patients with an inactivating mutation incretin-based therapy is superior (4, 5).

Conclusions: Meticulous documentation of the disease course, complications and response to therapy is necessary to improve our insight and management of the heterogeneous

disease that MODY12 comprises. We also conclude that considering the diagnosis of MODY and demanding genetic testing in certain patients can be of importance, as it can guide therapeutic decisions.

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A case of a heterozygous inactivating *CASR* variant with adult-onset symptomatic hypercalcemia requiring extensive surgery

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Abstract

We describe the case of an adult female patient with symptomatic familial hypocalciuric hypercalcemia requiring a step-wise therapeutic approach and the eventual need for a total parathyroidectomy and thyroidectomy to cure symptoms. Genetic analysis demonstrated a heterozygous R227L inactivating *CASR* gene variant, previously only described in neonatal severe hyperparathyroidism. Postoperative histology showed diffuse hyperplasia of all four parathyroid glands along with the presence of intrathyroidal parathyroid tissue. With regard to clinical management this case suggests that familial hypocalciuric hypercalcemia should be classified as an atypical form of primary hyperparathyroidism rather than a distinct entity.

Case presentation

A 42-year old woman consulted the general practitioner with a 4-month symptomatology of diffuse muscle cramps, tiredness, nausea, and constipation. Symptoms worsened with exercise. Biochemistry at presentation showed a marked PTH-mediated hypercalcemia along with a decreased fractional calcium excretion (cf Table 1). No serum calcium had been determined in earlier years. Neck ultrasonography showed no parathyroid glands. Bone mineral densitometry showed osteopenia. Parathyroid scintigraphy showed discrete tracer accmulation at the lower pole of the right thyroid lobe.

Sequencing analysis of the CASR gene on peripheral blood-derived DNA showed a heterozygous variant NM_001178065.1:c.680G>T (p.Arg227Leu/R227L) in exon 4 of CASR Under treatment with intravenous rehydration serum calcium and symptomatology were controlled, but relapsed after cessation of IV fluid. Because of symptomatic PTH-mediated hypercalcemia and dubious scintigraphy, a surgical neck exploration was planned. Surgery showed four mildly enlarged parathyroid glands in situ. Parathyroid A, C, and D were resected. Histology showed lipomatous parathyroid tissue with discrete hyperplasia. Persistent marked hypercalcemia and PTH elevation were present in the postoperative phase. Because of progressive symptomatology (muscle cramps and tiredness) Cinacalcet was started, resulting in effective lowering of the serum calcium. However, this treatment had to be interrupted because of intolerance. A definitive treatment by totalisation parathyroidectomy was carried out. Because of the macroscopic normal appearance of the remaining parathyroid B and negative neck exploration for surnumeric or ectopic parathyroid

glands, also a total thyroidectomy was performed. Histologic examination confirmed lipomatous parathyroid tissue with mild hyperplasia, but also unraveled ectopic parathyroid tissue in the left mid and lower pole of the thyroid.

Hypercalcemia resolved after the second surgery, along with resolution of muscle cramps, gastro-intestinal symptoms, and tiredness.

The resulting hypoparathyroidism and hypothyroidism were treated with calcium supplementation, cholecalciferol, alphacalcidol and Levothyroxine. Currently, she is 3 years post-operative, with normal calcemia and TSH under her substitution treatment and without noticeable symptoms.

Discussion

This report describes for the first time a patient with FHH due to a heterozygous R227L variant in the CaSR gene with adult-onset symptomatic hypercalcemia.

In this case surgical therapy was opted for because of the presentation with symptomatic and biochemically overt PTH-related hypercalcemia.

The course of the case presented supports the theory to define FHH as an atypical presentation of PHPT. [1] The patient had multiple characteristic features of PHPT. Elevated PTH and parathyroid hyperplasia represent failure of suppression of the chief cell by chronic hypercalcemia, which defines PHPT. After ¾ parathyroidectomy, the patient had persisting symptomatic hypercalcemia and it was only after total removal of parathyroid tissue that durable remission of the symptoms occurred. Hence hypercalcemia was dominantly PTH-dependent rather than secondary to abnormal renal calcium handling. [1] The patient is cured and free of symptoms, but at the expense of chronic hypoparathyroidism and hypothyroidism necessitating lifelong supplementation.

The challenge and complexity of this case is that by opting for (sub)total parathyroidectomy the issue of symptomatic hypercalcemia is potentially replaced, by an issue of symptomatic hypocalcemia. Prior to proceeding to extensive parathyroid surgery, it is therefore primordial to discuss the risks, benefits, and uncertainties with the patient, in order to take a shared clinical decision. The risk of persistent symptomatic hypercalcemia in case of minimal parathyroid surgery should be balanced against the risk of chronic hypoparathyroidism, in case of total parathyroidectomy. In our case the patient is free of symptoms under standard treatment with calcium supplements and active vitamin D analogs, but of course she needs lifelong follow-up including screening for long-term complications of hypoparathyroidism according to the guidelines [2,3].

This case also underlines that potential intrathyroidal parathyroid localization should be taken into account during surgery, especially when bilateral neck exploration fails to identify a missing gland or adenoma. [4,5]

In the presented case, we show also that the genotype–phenotype correlation in inactivating mutations in *CASR* does not always hold.

In conclusion, this report shows that in adult cases of FHH surgery can be a necessary treatment modality depending on symptoms and complications, and supports classification of FHH as a form of hereditary primary hyperparathyroidism.

Table 1.

	Admission	¾ PTX +5 days	+ Cinacalcet +1 month	Cinacalcet stop	Total PTX +1 day *	total PTx +1 month**	total PTx + 1 year **
Serum							
Ca (mmol/L) 2.15-2.50	**3.08**	**3.09**	2.41	**2.94**	2.20	2.22	2.33
P (mmol/L) 0.87-1.45	0.78	0.70	0.90	0.84	1.29	1.12	1.11
PTH (ng/L) 15.0–65.0	**80.9**	**85.4**	41.1	**56.8**	**6.2**	16.3	13.12
eGFR mL/min/1.73m^2	>60	>60	>60	>60		>60	>60
25-OH Vit D (ng/mL) >20	24.1	24.5	-	-	17.6	25.5	23.6
Urine							
Ca (mmol/L) 2.50-7.50	4.82						2.76
FE Ca/Creat	**0.0087**						0.0116

*Under suppletion with Ca^{2+} 1000 mg/d

******Under suppletion with 1 µg alphacaldidol + Ca^{2+}1000 mg+ 800 IE cholecalciferol.

PTX: parathyroidectomy; PTH: Parathyroid hormone; Ca: calcium; P: phosphate; eGFR: estimated glomerular filtration rate (CKD-EPI) FE Ca/Creat: fractional urinary calcium excretion

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