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001

Androgen Insensitivity Syndrome can be due to a dimerization defect in the androgen receptor

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Mutations in the androgen receptor (AR) are associated with androgen insensitivity syndrome (AIS). Most AIS mutations affect either hormone, DNA or coactivator binding to the AR, but for some mutations there was no explanation yet. Recently, a crystal structure revealed a possible dimerization interface in the ligand binding domain (LBD) of the AR.[1] To test the physiological relevance of this LBD dimerization, we generated a mouse model with a W732R mutation located in this interface (further called AR Lmon). The male AR Lmon mice show an external phenotype with a blunt ended vagina, female ano-genital distance and nipple development. Analogous to complete AIS (CAIS), the AR Lmon mice do have intra-abdominal testes but did not developed other reproductive structures. These observations suggest that disruption of dimerization of the AR LBD is crucial for the functioning of the AR. Despite the female-like phenotype, serum concentrations of testosterone and androstenedione are extremely elevated (240 and 75 ng/dl, respectively). The 45-fold increase in serum LH suggests a disruption of the feedback in the hypothalamus-pituitary-gonadal axis, similar to patients with CAIS. The testes of AR Lmon mice show a phenotype that is intermediate between wild type (WT) and AR knock out mice (ARKO). Seminiferous tubules are intermediate in size, hyperplasia of Leydig cells (LC) is observed and despite disrupted functioning of the AR, elongated sperm cells can be found in AR Lmon testes. RNAseq analysis of testes confirmed the differences between WT, AR Lmon and ARKO. The LC-specific Insl3 gene is not expressed in AR Lmon mice. Expression levels of other AR-regulated genes are also reduced, while enzymes involved in androgen synthesis are increased, except for 17-beta-hydroxysteroid dehydrogenase (Hsd17b3), which is responsible for the conversion of androstenedione into testosterone. Luciferase reporter constructs revealed that the Hsd17b3 promotor is controlled by the AR. In bone, however, the phenotype is comparable to ARKO with reduced trabecular and cortical bone. In conclusion, a mouse model of the W732R mutation phenocopies human CAIS, despite the fact that *in vitro* this mutant AR still can transactivate reporter genes. The corresponding mutation in the human AR was found in two siblings with androgen insensitivity.[2] The mouse model also revealed that the AR regulates the final step in testosterone synthesis as it controls the expression of Hsd17b3.

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002

Sexual Dimorphism in bone size is mediated by neuronal ER alpha (ERα) signaling in females during late puberty

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Introduction

Pubertal sex steroids are indispensable for peak bone mass acquisition as well as skeletal sexual dimorphism. In males, both androgen receptor (AR) and estrogen receptor alpha (ERα) are required for optimal periosteal cortical bone expansion, while estrogens limit bone size in females. In early puberty, estrogens directly stimulate longitudinal growth via ERα in cartilage, but also indirectly via growth hormone (GH) and insulin-like growth factor I (IGF-I). Estrogens in late puberty however, also exert direct inhibitory effects on growth plate cartilage, hereby limiting longitudinal bone growth. Recently, it has become more evident that there is possible neuroendocrine regulation of ERα on bone metabolism, since bone is highly innervated and ERα is enriched throughout the central nervous system. Here, we aimed to study to what extent neuronal ERα contributes to the estrogenic action on skeletal growth during puberty.

Materials and methods

ERα flox mice were crossed with Thy1-Cre mice to generate mice with specific, tamoxifen-inducible inactivation of ERα in extrahypothalamic neurons (N-ERαKO). Tissue-specific ERα deletion in the central nervous system was validated using qPCR. Serum E2/T were measured with gas chromatography/mass spectrometry (GC-MS). At 16 weeks of age, both cortical and trabecular bone morphology was analyzed by microCT. A three-point bending test was conducted to measure the mechanical strength of the femur. To assess potential contribution of GH signaling, serum IGF-I and IGFBP-3 were measured by an in-house RIA and ELISA, respectively.

Results

A tamoxifen-induced knockout at 6 weeks of age reduced ERα mRNA levels in both cerebral cortex and brain stem by 50%, while ERα expression was unaffected in hypothalamus and non-neuronal tissues. Serum T and E2 remained normal in both sexes, indicating that hypothalamus-pituitary-gonadal function was not affected by ERα disruption. Inactivation of neuronal ERα did not alter body weight in males, but female N-ERαKO were 6.3% heavier ($P < 0.01$) and 2% longer ($P < 0.05$) compared to control littermates. In female N-ERαKO mice, femoral and L5 vertebral lengths increased by 2.4% ($P < 0.01$) and 4.8% ($P < 0.01$) respectively. Radial bone expansion at femoral midshaft also increased in female N-ERαKO concomitantly with higher serum IGF-I as well as IGFBP-3, which is a marker of GH secretion. Furthermore, the three-point bending test revealed increased bone strength in female N-ERαKO compared to control littermates. In contrast, inactivation of neuronal ERα had no major effect on bone growth in males.

Conclusions

Neuronal ERα limits female bone size and strength. The potential indirect effect of estrogens on GH/IGF-1 signaling represents an additional central inhibitory mechanism of action of estrogens on growth.

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003

Impact of changes in muscle secretome in the improvement of glucose homeostasis induced by bariatric surgery

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Introduction

Type 2 diabetes results from insulin resistance and B-cell failure. Bariatric surgery is an effective therapeutic modality for type 2 diabetes. Indeed, it induces high remission rates through improved insulin sensitivity and secretion. While the critical role of skeletal muscle in glucose homeostasis has long been known, its role as an endocrine organ secreting peptides, called myokines, has recently been identified. Some of these myokines were shown to influence glucose homeostasis by modulating insulin sensitivity of skeletal muscle as well as insulin secretion and survival of B-cells. Yet, their impact in the dramatic improvement of glucose homeostasis induced by bariatric surgery is unknown.

Aims

To characterize the changes in myokines secretion induced by bariatric surgery and to determine their impact on muscle insulin sensitivity and insulin secretion by B-cells.

Methods

Obese insulin-resistant patients were clinically and biologically assessed before and 3 months after bariatric surgery, including a muscle biopsy for primary human muscle cells culture and RNA/protein analysis. Changes in myokines secretion will be identified with Liquid Chromatography tandem-Mass Spectrometry (LC-MS/MS) on culture media conditioned by muscle cells and with global mRNA sequencing of muscle samples, both obtained before and after surgery. These changes will be confirmed in the circulation by ELISA or Western-Blot and correlated with the parameters of glucose homeostasis (HOMA test) measured before and after surgery.

Results
Up to now, 32 patients have completed the study (16 women, 23 sleeve gastrectomies) whom 21 had muscle biopsies before and after surgery. Clinical and biological parameters including insulin sensitivity significantly improved after surgery ($P < 0.05$). Our primary muscle cells culture protocol provides well differentiated myotubes expressing myogenic transcription factors and myosin heavy chains as demonstrated by immuno-fluorescence and RTq-PCR. Conditioned culture media are being collected and concentrated to perform LC-MS/MS analysis while total RNA is currently being extracted from muscle samples and intended to RNA sequencing.
Conclusion
Bariatric surgery dramatically improves glucose homeostasis and insulin sensitivity. Our study protocol should allow i) the identification of myokines whose secretion is modified by bariatric surgery, ii) to test the action of some of these myokines on insulin sensitivity of muscle cells and on insulin secretion by B-cells in *in vitro* models.

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004

Misclassification of fractures by self-report: an analysis from the FRISBEE cohort

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Osteoporosis is a major public health problem that is responsible for a considerable morbidity, mortality and health care costs. Evaluation of fracture risk is essential to select patients who will benefit most of interventional strategies. Most prospective cohort studies, with fracture outcomes, rely on participant self-report as the main or only source of information on fracture incidence. Systematic validation by screening of medical files is time-consuming, costly and almost impossible to accomplish in large scale multicenter epidemiological studies. We found in a well characterized prospective population-based cohort of 3560 postmenopausal, volunteer women, aged 60–85 years, included in the Fracture Risk Brussels Epidemiological Enquiry (FRISBEE) cohort that the global rate of unconfirmed self-reported fractures ('false positives') was 14.4% (BES 2018 and ECTS 2019, Abstracts). Over a median follow-up period of 8.9 years, the global percentages of validated fractures were 77.1% for the four classical 'major osteoporotic fractures' (MOFs, ie. hip, vertebra, shoulder/upper arm, wrist), 75.4% for 'other major' and 53.6% for 'minor' fractures. The percentages of confirmed fractures varied by fracture site, with the hip having the highest proportion of confirmed fractures (90.3%, $n=65$), followed by fractures of the pelvic bone (88.5%, $n=46$), wrist and shoulder/proximal humerus (80.7%, $n=129$ and 80.8%, $n=84$, respectively). Participant self-report could also lead to bias in the classification of fracture status if a significant proportion of fractures are not reported. This other cause of misclassification has been little studied so far. We thus assessed the proportion of non-reported fractures ('false negatives') in order to evaluate the possible impact of this phenomenon in epidemiologic cohort studies and in models of fracture risk prediction. Participants are followed by yearly phone calls for the occurrence of incident fragility fractures. We had access to the medical records of 67.9% of our study participants. After a thorough verification of these medical records, we found a total of 209 unreported fractures. The false negative rate for all fractures was 21.1%, including 21.7% for the 4 MOFs, 13.1% for 'other major fractures' and 25.8% for minor fractures. The percentages of fractures showed to be 'false negatives' varied by fracture site: 1.4% ($n=1/73$) at the hip, 46.3% at the spine ($n=99/214$), 5.3% at the shoulder/proximal humerus ($n=5/94$) and 7.1% at the wrist ($n=11/154$). We analyzed participants' baseline characteristics that could have influenced the rate of 'false negatives' fractures. In a multivariate analysis, older subjects (OR 0.6; 95% CI, 0.9–2.4; $P=0.007$) and subjects with a lower education level (OR 1.6; 95%CI, 1.1–2.3; $P=0.008$) were more likely to underreport a fracture event. Besides 'false positive' reports, underreporting of a substantial proportion of fracture events is another major cause of misclassification of fracture events. Both types of inadequate reports will influence any model of fracture risk prediction and decrease statistical power when estimating the associations between candidate risk factors and incident fractures.

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005

Serum levels of Wnt-signalling parameters poorly reflect bone mass and metabolism in healthy boys and men

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Background
Bone turnover markers are used in research and clinical practice, but only in part reflect bone formation and resorption. Components of the Wnt-signaling pathway, regulating osteoblastogenesis and osteoblast function, can be measured in serum, however it is unclear whether they reflect underlying bone mass and metabolism.
Objective
Determine whether serum levels of Wnt-signalling components reflect bone mass or metabolism in men during growth and after attaining peak bone mass age.
Methods
Sclerostin, DKK-1 and OPG were measured in 108 healthy males (34.2 ± 4.9 years) from the SIBLOS cohort and 122 peri-pubertal boys from the NINIOS cohort (12.5 ± 2.8 years) using the quantitative sandwich ELISA method developed by Biomedica. Procollagen type 1 N-terminal propeptide (P1NP), carboxy-terminal collagen crosslinks (CTX) and osteocalcin were measured using ECLIA (Roche Diagnostics) in the SIBLOS cohort only. Dual-energy x-ray absorptiometry (Hologic) determined body composition and bone mineral content (BMC) at the whole-body and lumbar spine.
Results
In NINIOS, DKK-1 concentrations were higher than in SIBLOS (54.05 pmol/l, 33.45 pmol/l, respectively; $P < 0.001$), whereas OPG levels were non-significantly lower (3.50 pmol/l, 3.76 pmol/l, respectively; $P=0.07$). No differences were found for sclerostin. No association between lumbar or whole-body BMC with Wnt-signalling parameters was found. In SIBLOS, no associations were found between P1NP, CTX, and osteocalcin on the one hand and sclerostin, OPG and DKK-1 on the other hand.
Conclusion
Serum levels of sclerostin, OPG and DKK-1 were not related to bone mass in either peri-pubertal boys or adult men. Further, in adult men, they did not associate with P1NP, CTX or osteocalcin. However, as peri-pubertal boys showed higher levels of DKK-1 than adult men, DKK-1 being reflective for bone modelling cannot be ruled out. This will be addressed in the longitudinal part of the NINIOS study and by determining P1NP, CTX and osteocalcin in the NINIOS cohort.

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006

Endocrine consequences of immune checkpoint inhibitors

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Immune checkpoints inhibitors have fundamentally changed the management of oncologic patients. These treatments consist of monoclonal antibodies directed against CTLA-4 (cytotoxic T-lymphocyte antigen 4), PD-1 (programmed cell death protein-1) and PD-L1 (one of its ligands). By blocking these receptors or ligands, the antibodies reverse the immune tolerance induced by the cancerous cell on the T-lymphocyte and favour lymphocytic reactivation and anti-tumor activity. Immune tolerance to auto-antigens is maintained with the help of these checkpoints. Targeting them can lead to auto-immune side effects. These latter mostly impact the cutaneous and digestive system, but the endocrine glands are not spared.
Aim of the work
The aim of this retrospective study was to establish the prevalence and characteristics of endocrine immune-related adverse events in order to provide monitoring and treatment algorithms.
Methods
We identified patients who developed biological hormonal anomalies during their immunotherapy treatment at Liège University Hospital. We collected data regarding the types of cancers treated with immunotherapy, the treatments administered, the time to onset of adverse events and their clinical presentation. We also recorded information on the treatment of these side effects and their evolution.
Results
1277 patients were identified from the electronic medical records, with keywords corresponding to the names of the different immunotherapies. Of these patients,

434 were actually treated with the molecules of interest between the 1st of January 2009 and the 31st of December 2018. 113 patients with biological anomalies compatible with endocrine immune-related adverse events were found. Thyroid function anomalies and hypophysitis were the most frequent endocrine side effects. No cases of adrenalitis, autoimmune diabetes or parathyroiditis were identified. In our study population, 22.3% of patients (97/434) presented an alteration of the thyroid function. It was more frequent with combined treatments (47.3% of the patients on anti-CTLA-4 and anti-PD-1) and with anti-PD-(L)1 molecules (20.1%). Hypothyroidism can occur following transitory hyperthyroidism. Hypophysitis was shown in 5.3% of patients (23/434). It was mostly due to combined treatment (36.8% of the patients treated with the association) and to anti-CTLA-4 therapies (7.7%). Pituitary damage led to hormonal deficiency. Central adrenal insufficiency was observed in 73% of these patients followed in frequency by hypogonadotropic hypogonadism (56.5%) and central hypothyroidism (30.4%). Recovery of the thyroid and gonadal axes was encountered in 57 and 46% of cases respectively. The recovery is inconstant and does not depend on the administration of systemic glucocorticoids.

Conclusions

Endocrine immune-related adverse events are frequent and can be severe. An early diagnosis and, consequently, the appropriate management would help reduce the morbidity, sometimes even the mortality and would allow to pursue the immunotherapy.

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007

Low dose continuous IV etomidate for severe Cushing's syndrome in the non-critical care setting: a clinical study

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Introduction

Severe Cushing's syndrome (CS) is defined by extremely high serum cortisol levels (usually >1000 nM), along with severe and deadly complications, including sepsis, heart failure, acute psychosis, vascular thrombosis, digestive haemorrhage and bowel perforation. Rapid control of such hypercortisolism is mandatory and has been shown to decrease operative mortality and complications. Oral treatments such as ketoconazole and metyrapone are often inadequate in the face of life threatening complications and limited oral intake possibilities. Etomidate is a hypnotic agent widely used in general anaesthesia induction, while also being one of the most potent inhibitors of 11-B-hydroxylase and therefore of cortisol secretion[i]. Low dose continuous intravenous (IV) infusion of etomidate has been shown to rapidly decrease cortisol levels in patients with severe CS in the ICU setting[iiiii], without causing harmful side effects (myoclonus or adrenal crisis) A safe use of etomidate has been also suggested for similar indication in the non-ICU setting[iv].

Aim of the work

We retrospectively analysed the efficacy and safety of low dose IV etomidate infusion in five patients with severe and complicated CS treated in our (non ICU) Endocrinology unit between 2012 and 2018.

Main results

All five patients were male, with an average age of 53.4 years, and all had cancer: Three had cortisol secreting adrenal carcinomas and two had ectopic ACTH secretion from a malignant neuro-endocrine tumour. All patients had several complications before treatment, including infections, vascular thrombosis, cardiac failure, severe hypertension and/or uncontrolled diabetes. Median cortisol levels on admission were 1288 nM (range 751–2301 nM) (Figure 1). Etomidate (Hypnomidate® 20 mg/10 ml propylene glycol solution, Janssen pharmaceuticals) was administered through a peripheral IV catheter at a starting dose of 0.03 mg/kg/h. Infusion rate was then adjusted by 0.5 mg/h increments in order to achieve morning cortisol levels between 200 and 300 nM. Mean effective etomidate rate was 3 mg/h and the average number of days before reaching cortisol levels <500 nM was 4.2. Median morning cortisol level upon discontinuation of etomidate was 306 nM (range 183–479 nM). No adverse effect related to treatment was noted (in particular no somnolence) and no propylene glycol related adverse effects were noted (no renal failure, phlebitis, or haemolysis). Four out of five patients survived after etomidate discontinuation, being subsequently treated by primary tumor resection, mitotane and/or bilateral adrenalectomy. The single patient who died had a 16 cm adrenal tumour with peritoneal carcinomatosis and a poor performance status (ECOG 3–4) that precluded surgery or chemotherapy. The decision was made, together with the patient and his family, to stop etomidate and enter palliative care.

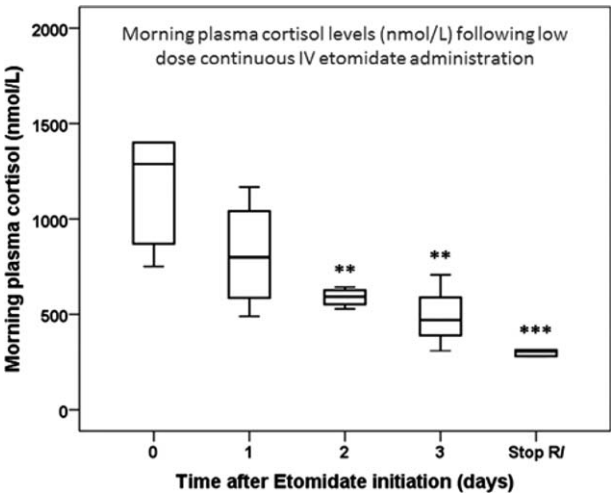

Figure 1.

Conclusion

We report a case series of 5 patients treated in a non-intensive care unit with low dose continuous IV etomidate for severe and complicated Cushing's syndrome. Treatment was rapidly successful in reducing cortisol levels below 500 nmol/l within 3–5 days and did not result in any treatment related adverse effects.

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008

Study of neuroendocrine deficits in a series of 74 patients following traumatic brain injury

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Aim of the work

Clinical research studies over the last 15 years have reported a significant burden of hypopituitarism in survivors of traumatic brain injury (TBI). However, these endocrine anomalies remain under diagnosed due to nonspecific clinical signs and misunderstanding of the phenomenon. The aim of the work is to evaluate for the first time in Belgium their prevalence and to quantify the deficits of the different pituitary axes in patients recruited to the endocrinology consultation of a university center.

Main results

We studied the data of 74 patients. The prevalence of neuroendocrine disorders in this series is 37.84% (28/74). The biological explorations found: somatotropic deficits (19/28), gonadotropic deficits (9/28), corticotropic deficits (8/28), thyrotrophic deficits (3/28), prolactin deficiency (3/28), prolactin excess (1/28), and diabetes insipidus (1/28). Deficiencies are most often isolated (19/28) rather than associated (9/28). Isolated somatotropic deficiency is the most common (12/28, 42.86%). TBI patients with endocrine deficiencies had significantly higher BMI (30.14 ± 4.62 versus 24.62 ± 4.62 kg/m^2, $P<0.001$) than TBI patients without hormonal deficiencies. This can be partly explainable by body composition changes induced by GH deficiency. Indeed, the median BMI of our patients with somatotropic deficiency is significantly higher than in the other patients, while there is no significant difference in BMI for the other deficits. It should be noted that there are not enough cases of disorders of the lactotropic axis and diabetes insipidus to assert a statistically significant difference.

Conclusion

TBI and their consequences are a major public health problem, and hypopituitarism occurs in about 1/3 of cases. No formal risk factors have been identified but it seems that the severity of the trauma is often related to the occurrence of post-traumatic hypopituitarism, although they are encountered in a significant number of mild head injuries. The primary lesions are mechanical and the secondary lesions are vascular. Brain imaging can show lesions or be normal. Most often, only one pituitary axis is affected, and most frequently the somatotropic axis. Deficits can resolve or have a delayed onset. The signs and

symptoms of post-traumatic hypopituitarism are most often nonspecific, so that they are not frequently detected. Their prevalence would be underestimated, and their routine screening could ensure that non-tumor causes of hypopituitarism exceed tumor causes.

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009

Risk of Malignancy of the Thyroid Nodule Evaluated by Scintigraphy

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Background
Thyroid nodules are a common finding in clinical practice. Among classic risk factors for thyroid cancer, thyroid scintigraphy has traditionally been attributed prognostic value, with cold nodules implying greater risk. However, research supporting this assumption is of considerable age and possibly influenced by selection bias. In this study, we aimed to calculate the risk of malignancy in cold and hot nodules.
Material and Methods
All thyroid nodules that underwent both thyroid scintigraphy and pathologic characterisation (cytology and/or histology) in a 5-year period at a tertiary centre were retrospectively analysed. Cancer rates were calculated in cold and hot nodules. Furthermore, rates of malignancy were calculated taking into account several established and more controversial risk factors for thyroid carcinoma, in order to identify subgroups with greater risk for cancer.
Results
343 thyroid nodules were included for study. Cancer rates were 7.7% in cold nodules ($N=248$) and 5.3% in hot nodules ($N=95$). Thyrotropin levels were lower in hot nodules ($P=0.000$), and levels were higher in cancerous cold nodules compared with benign cold nodules ($P=0.014$). A cancer rate of 26.7% was noted in cold nodules with elevated anti-thyroglobulin levels. In all other subgroup analyses, the rate of malignancy in cold nodules was never higher than cancer rates suggested by literature for nodules in the general population. Although similar observations were made for hot nodules, no definite conclusions were drawn as there were too few hot nodules to perform statistical tests.
Conclusion
Our findings suggest that cold nodules are not high-risk nodules by definition, as their cancer rates were not notably higher than the risk of malignancy proposed in literature for nodules in the general population. Therefore, we discourage the use of thyroid scintigraphy for the selection of cold nodules for further pathologic characterisation.

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010

Effect of nationwide reimbursement of sensor-augmented pump therapy in a paediatric type 1 diabetes population on HBA1C, hypoglycaemia and quality of life: The rescue-paediatrics study

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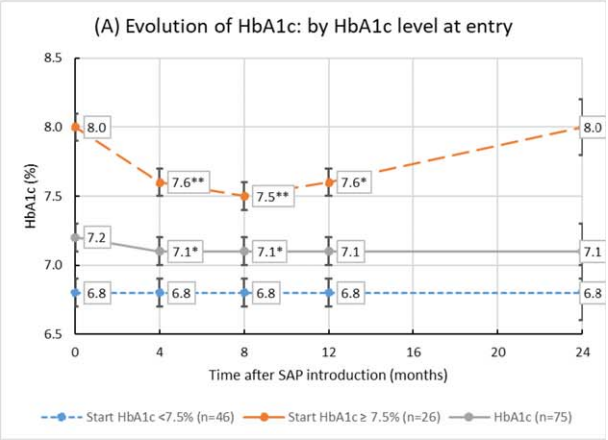
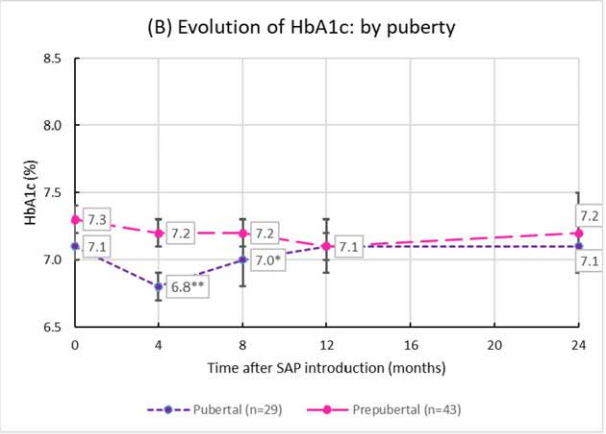
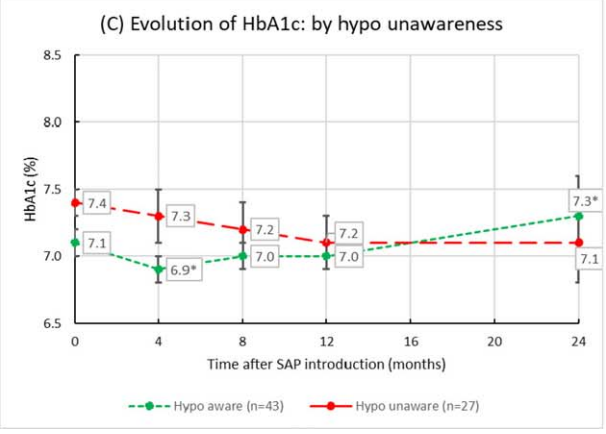
[*]Joint First Authorship; [†]Joint Last Authorship; [‡]RESCUE study, ClinicalTrials.gov: NCT02601729.

Background
Long-term real-life data of sensor-augmented pump therapy (SAP) in paediatric type 1 diabetes (T1D) patients are lacking.

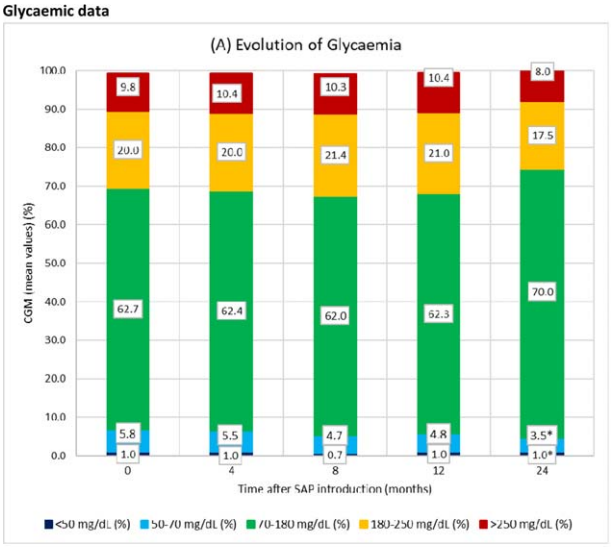
HbA1c data



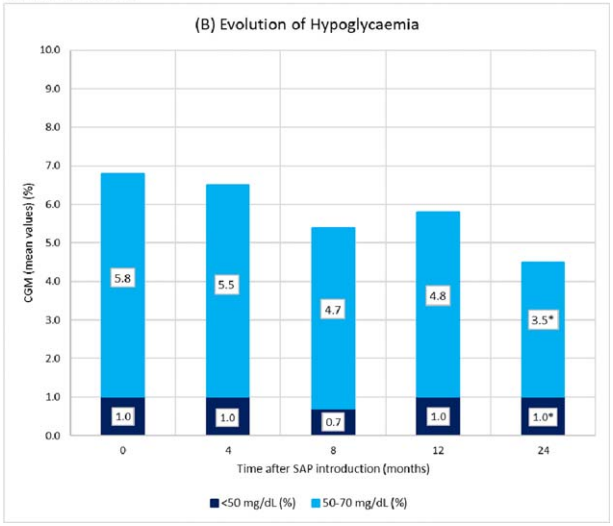




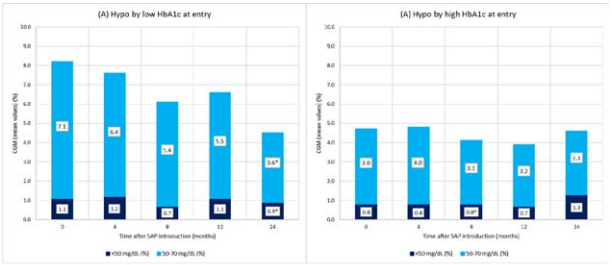
Glycaemic data

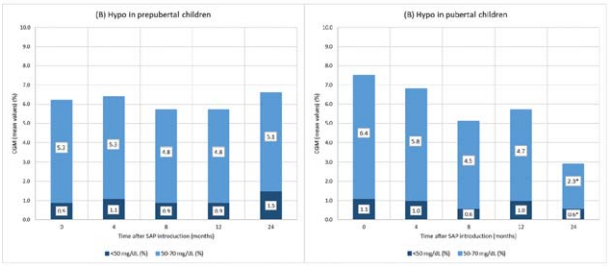


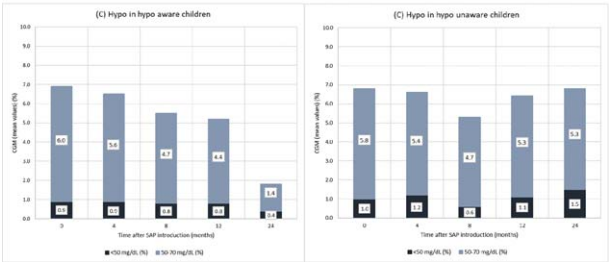
Hypoglycaemia data



Objectives
To assess the impact of SAP in a nationwide study of paediatric T1D patients on HbA1c, hypoglycaemia and quality of life until 24 months.
Methods
Between December 2014 and February 2017, 75 children entered the Belgian reimbursement system for SAP and were followed for 12 ($n=73$) and 24 months (sub analysis of the children of the University Hospital of Antwerp; $n=25$). Study endpoints included evolution of HbA1c, hypoglycaemia and quality of life (impact, satisfaction, worry and parents' questionnaires).
Results
Seventy-three (97%) patients used SAP for 12 months. Baseline HbA1c (7.2±0.7%) decreased to 7.1±0.8% at 4 months ($P=0.02$), remained stable at 8 months (7.1%±0.7%; $P=0.03$) and 12 months (7.1%±0.8%; $P=0.1$), even after 24 months (7.1±0.9%; $P=0.4$). Patients with a baseline HbA1c <7.5% ($n=46$), had a mean HbA1c of 6.8±0.5% and it did not change after 4, 8, 12 and 24 months ($P=$NS). Subjects with a baseline HbA1c ≥7.5% ($n=26$, mean HbA1c 8.0±0.4%) showed an improvement of 0.4% at 4 months (7.6±0.7%; $P=0.002$), an improvement of 0.5% at 8 months (7.5±0.6%; $P=0.001$), with a stabilisation at 12 months (7.6±0.7%; $P=0.03$). No improvement was seen after 24 months in the remaining seven children with a poor metabolic control (8.0±1.0%; $P=0.9$). Time in hypoglycaemia (50–70 mg/dl) decreased from 5.8±5.1% at baseline to 4.8±3.2% at 12 months ($P=0.07$) and to 3.5±4.0% at 24 months ($n=20$; $P=0.009$). Time in severe hypoglycaemia (<50 mg/dl) did not change over time (1.0±1.6%). Overall, quality of life did not change in our patients while using SAP.







Conclusions
Reimbursement of SAP in paediatric T1D patients improved HbA1c, especially in patients with a poor metabolic control, and decreased time in hypoglycaemia without affecting overall quality of life.

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011

Effect of exogenous testosterone administration on serum oestradiol levels in assigned female at birth transgender people: result from a large transgender cohort.

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Aim
The changes in serum oestradiol levels in assigned female at birth (AFAB) transgender people receiving testosterone therapy have not been elucidated. How serum oestradiol levels change after initiation of testosterone therapy, if these levels should be monitored and whether altered oestradiol levels will result in adverse health outcomes, remains unclear.
Methods
This prospective cohort study was part of the European Network for the Investigation of Gender Incongruence (ENIGI). Serum levels of sex steroids and

body composition were prospectively and cross-sectionally assessed in 746 AFAB transgender people during a three-year follow-up period, starting at the initiation of hormone treatment.
Results
Oestradiol levels decreased from 45.49 [24.00–102.15] pg/mL (baseline, median [percentile 25–percentile 75]) to 36.5 [25.0–46.2] pg/mL over three years ($P<0.001$), a change was already noticeable during the first three months (mean −17.13 pg/ml, 95% CI −23.82 – −10.56, $P<0.001$). Serum oestradiol levels were lower in people without endogenous oestradiol production (contraceptive users or people who underwent gonadectomy) at baseline and after three months, compared to people with endogenous oestradiol production (contraceptives: $P<0.001$, gonadectomy: $P=0.007$). The use of long acting testosterone undecanoate injections resulted in a more prominent decrease in serum oestradiol values over twelve months, compared to short acting mixed testosterone esters injections ($P<0.001$) or testosterone gel ($P=0.001$). Changes in serum oestradiol were positively correlated to changes in LH ($\rho=0.107$, $P<0.001$) and negatively correlated to changes in FSH levels ($\rho=-0.167$, $P<0.001$) and BMI ($\rho=-0.082$, $P<0.001$).
Conclusion
Testosterone administration in AFAB transgender people results in decreasing serum oestradiol levels. Although an underlying mechanism is difficult to fathom, our results suggest that testosterone administration may suppress endogenous oestradiol production. However, serum oestradiol levels in AFAB people receiving testosterone therapy remain higher than levels observed in males, which may be attributed to aromatization of exogenous testosterone.

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012

Evolution of circulating thyroid hormone levels in preterm infants during the first week of life: Perinatal influences and impact on neurodevelopment

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Aim
For several decades, transient hypothyroxinemia of prematurity is topic of debate. The pathophysiology is incompletely understood and consensus on the therapeutic approach is lacking. This study aimed to obtain more insight in the pathogenesis by studying trends in thyroid hormone levels during the first week of life.
Methods
This single-center prospective observational study studied plasma levels of total and free T4, total T3, TSH and TBG in cord blood and at the end of the first week of life in 120 preterm infants (gestational age < 37 weeks). The change over time was calculated (delta, Δ). The impact of perinatal and subsequently postnatal variables on Δwas studied by hierarchical multiple regression. The impact of Δ on the neurodevelopmental outcome at the corrected age of 9 and 24 months, measured by the Bayley Scale of Infants Development II, was assessed by logistic regression.
Main results
Δ(f)T4 levels were negatively affected by gestational age and use of dopamine, whereas only gestational age was associated with low ΔT3 levels. Negative Δ(f) T4 levels were present in 75% of the extremely-low-for gestational-age infants, whereas 23·5% had a negative Δ T3 level. There was an increased risk for an abnormal mental developmental score (<85) with decreasing ΔT3 at 9 months, corrected age, but not at 24 months.
Conclusions
A negative evolution in circulating thyroid hormone levels is principally an immaturity phenomenon, whereas dopamine can further suppress the hypothalamic-pituitary-thyroid axis. There is at least a temporary negative effect of this evolution on the infants' neurodevelopment.

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013

The interpretative value of CGM-derived parameters in type 1 diabetes depends on the level of glycaemic control

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Background and aims
HbA1c as a gold-standard measure for glycaemic control has been criticized for several years: lacking the ability to capture hypoglycaemia, time spent in different glucose ranges or to reflect glycaemic variability (GV) are frequently reported shortcomings. Continuous glucose monitoring (CGM) can overcome this, and several new CGM-derived parameters have been proposed to provide additional insights, with the concept of time in range (TIR) and other parameters reflecting glycaemic control and variability being put forward. In this study, we aimed to examine the (inter)relation between these new promising parameters and other indices of glycaemic control in a group of T1DM patients.
Methods
In this observational study, ninety-eight T1DM patients with a minimum disease duration of 10 years and without known macrovascular complications were enrolled in a screening program. Patients were equipped with a blinded Dexcom G4 CGM device for seven days. TIR was defined as time spent in glucose range of 70–180 mg/dl, time in hypoglycaemia was subdivided in total (<70 mg/dl) and level 2 (<55 mg/dl); and time in hyperglycaemia in total (>180 mg/dl) and level 2 (>250 mg/dl). GV was determined by coefficient of variation (COV: mean blood glucose (MBG) divided by S.D. of glucose values). Pearson correlations were used to examine associations between these parameters.
Results
95 patients (age: 45±10 years; HbAc1: 7.67±0.75%) were included in CGM data analysis (MBG: 159±31; TIR 56.1±14.9%; COV: 43.4±7.8%). Nineteen patients showed good glycaemic control with HbA1c values <7%, 46 patients moderate (7–8%) and 30 patients poor glycaemic control (HbA1c >8%). As expected, HbA1c was significantly associated with MBG ($r=0.483$; $P<0.001$) and time spent in hyperglycaemia (total: $r=0.509$; level 2: $r=0.470$; $P<0.001$), but not with time in hypoglycaemia and COV, even after analysis in HbA1c subgroups. In the entire cohort, TIR was negatively associated with HbA1c ($r=-0.508$; $P<0.001$), MBG ($r=-0.851$; $P<0.001$) and time spent in hyperglycaemia (total: $r=-0.924$; level 2: $r=-0.855$; $P<0.001$), but not with time spent in hypoglycaemia. However, subgroup analysis showed that TIR did associate with shorter time in level 2 hypoglycaemia in patients with good ($r=-0.596$; $P=0.007$) and moderate ($r=-0.252$; $P=0.047$) glycaemic control. In contrast, COV was strongly positively associated with time in hypoglycaemia (total: $r=0.750$; level 2: $r=0.740$; $P<0.001$), but not with time in hyperglycaemia. Once more, subgroup analysis showed that COV did correlate with time in hyperglycaemia in the lowest HbA1c group (total: r: 0.588; level 2: $r=0.662$; $P<0.01$) and with time in level 2 hyperglycaemia in the moderate group ($r=0.285$; $P=0.024$). The relationship between TIR and COV was modulated by HbA1c levels as well. TIR did not correlate with COV in the whole group. However, TIR was negatively associated with COV again in patients with good ($r=-0.832$, $P<0.001$) and moderate ($r=-0.469$, $P<0.001$) glycaemic control.
Conclusion
This study provides arguments for the added value of using CGM-derived parameters as TIR and COV in evaluating glycaemic control in T1DM patients, as they relate with clinical important situations such as level 2 hyper- and hypoglycaemia respectively. It should be noted however, that the interpretation and interrelation of these parameters depends on the level of glycaemic control of the individual patient, adding less in those with poor glycaemic control as it seems not to reflect hypoglycaemia or GV.

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014

No deleterious effect of pretreatment with everolimus and/or sunitinib on the subacute hematotoxicity of 177Lu-DOTATATE PRRT

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Background
Treatment of neuro-endocrine tumors (NETs) is often challenging, given the heterogeneity of primary tumor sites, the individual disease complexity and the variety of treatment options. If patients are progressive during first-line treatment with somatostatin analogues (SSA), peptide receptor radionuclide therapy (PRRT) is a validated treatment for somatostatin receptor overexpressing neuroendocrine tumors. The NETTER-1 trial has demonstrated a pronounced positive effect on progression-free-survival of PRRT compared to high dose SSA, with a strong tendency towards overall survival benefit. In our PRRT cohort, many patients are pretreated with targeted agents, due to requirements for reimbursement within the Belgian healthcare system. The mTOR-inhibitor everolimus is approved for treatment of primary pancreatic NET and non-functional gastrointestinal or pulmonary NET. The multiple tyrosine kinase inhibitor sunitinib is approved for pancreatic NETs. Both targeted agents significantly improve progression-free survival, but they can entail several side effects, including bone marrow depression. There is currently only limited data regarding the optimal sequence of approved treatments in NET after failure of first line SSA.
Aim
Our aim was to determine the influence of pretreatment with everolimus and/or sunitinib on the subacute hematotoxicity of PRRT. We hypothesized that previous treatment with these agents could potentiate the subacute hematotoxicity of PRRT. This might also be clinically relevant for long term effects, since subacute hematotoxicity after PRRT has been shown to be a risk factor for late hematotoxicity (persistent hematological dysfunction and/or leukemia), one of the major side effects of PRRT.
Materials and methods
We performed a single-center retrospective study in which we analyzed consecutive patients treated with 177Lutetium-DOTATATE PRRT (1 to 4 cycles of 7.4 GBq), between November 2013 and July 2018. 177 Lutetium is a β-particle emitting radionuclide, with a mean penetration range of 0.7 mm in tissue (maximum penetration range of 2.2 mm), which is sufficient to kill targeted tumor cells and tumor cells in the vicinity ($\sim$20 cell diameters), with a limited effect on more distant normal cells. DOTATATE is a peptide that binds with high affinity to the somatostatin receptors overexpressed in NETs. Patients were assigned to two groups according to their pretreatment: no targeted agents ($N=41$), or pretreated (with everolimus, sunitinib or both; $N=41$). The end point was subacute hematotoxicity, defined as the nadir value in the timeframe from first administration until 3 months after the last administration, using the CTCAE 4.03 classification.
Results
The primary tumor site was gastroenteropancreatic in 80% of the patients. No statistically significant differences in severe acute hematotoxicity were seen in the pretreated group vs. the naïve group for hemoglobin (grade 3/4: 12% vs. 22%), neither for leucocytes (grade 3/4: 10% vs. 7%), nor platelets (grade 3/4: 15% vs. 15%). Limitations of this study are its retrospective nature, potential bias in the lack of use of targeted agents in patients more susceptible to toxicity, and the limited number of patients and events.
Conclusion
In a cohort of patients pretreated with everolimus and/or sunitinib, we could not demonstrate a significant negative influence of everolimus or sunitinib pretreatment on the subacute hematotoxicity of 177Lu-DOTATATE PRRT. With regard to the optimal sequence of approved treatments in NET after failure of first line SSAs, this study does not provide arguments to place everolimus and/or sunitinib treatment after PRRT.

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015

Impaired hypoglycemia awareness in children and adolescents with type 1 diabetes

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Aim of the work
Impaired Hypoglycemia Awareness (IHA) is associated with an increased risk of Severe Hypoglycemia (SH) in adults with diabetes but is less known in youth. The purpose of this study was to determine the prevalence of IHA and its clinical characteristics in a cohort of children and adolescents with type 1 diabetes.
Methods
This prospective observational study of two-month duration included all eligible subjects with type 1 diabetes attending our center, aged from 4 to 20 years. IHA was defined by a score ≥ 4 on the Gold scale. For the aim of this study, SH was defined as an event leading to loss of consciousness. SH were collected by reviewing the patients' logbook and adjudicated by an endocrinologist. Quality of life (QoL) was determined by mean of the 3-level version of the EuroQol instrument.
Main results
On the 404 subjects included, 128 (31.7%) were diagnosed with IHA. Among these, 21% experienced at least one SH vs 11% of patients without IHA during the study period ($P=0.009$). Subjects with IHA were younger (median [IQR]) (12.9 [10.4–16.3] vs 14.2 [11.7–16.9] years; $P=0.025$), younger at diabetes diagnosis (6.2 [3.5–9.3] vs 8.0 [5.0–11.2] years; $P=0.001$), more often c-peptide negative (78 vs 67%; $P=0.037$) and female (57 vs 44%; $P=0.014$) than subjects without IHA. There were no differences in diabetes duration (5.3 [2.8–8.5] vs 6.2 [3.6–8.6] years), in HbA1c (7.6 [7.0–8.5] vs 7.7 [7.1–8.6] %) or in nocturnal occurrence of SH (8.7 vs 5.7%). Subjects who experienced at least one SH were 2.9 times more likely to exhibit IHA ($P=0.008$) and decreasing QoL was associated with an increased likelihood of IHA. Subjects with IHA performed more glucose controls (7.0 [4.0–10.0] vs 6.0 [4.0–8.5] per day; $P=0.046$).
Conclusions
A significant proportion of youth with type 1 diabetes have IHA. Screening for IHA should be an important part of routine diabetes care in children, as IAH is associated with SH.

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016

Is it worthwhile to distinguish between grade 1 and grade 2 subclinical hyperthyroidism for alteration of metabolic parameters?

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Aim of the work
The effects of subclinical hyperthyroidism (SCH) on bone and heart have been well documented. Effects on other parameters like lipids metabolism and weight regulation have also been reported but mainly in cross-sectional studies. The potential benefits of treatment of endogenous subclinical hyperthyroidism are more controversial as few large controlled studies on clinical outcomes have been performed. ATA guidelines recommend treatment according to the severity of the disease (grade 1 SCH (TSH between 0.10 and 0.39 mU/l) or grade 2 SCH (TSH $<$ 0.10 mU/l) and clinical parameters (age, menopausal status, cardiovascular disease, osteoporosis…). The aim of our work was to evaluate changes in body weight and lipids parameters following radioiodine treatment in patients with SCH caused by benign nodular goiter and to compare the results obtained in grade 1 and grade 2 SCH.
Methods
All of the 146 files of patients with nodular goiter treated by radioiodine for SCH between January 2008 and July 2018 and who had a follow-up in Erasme Hospital were retrospectively reviewed and separated into two groups according to their pre-treatment thyroid status: one group with pre-treatment grade 1 SCH and one group with pre-treatment grade 2 SCH. 58 patients were excluded from the study. The causes of exclusion were: cancer including thyroid cancer ($n=24$), death during follow up ($n=2$), any condition likely to affect weight changes during follow-up such as corticoids treatment ($n=16$), or other causes ($n=16$). TSH levels, evolution in weight and serum lipids values were recorded up to 3 years after radioiodine treatment. Patients were included in the study if at least one body weight was reported in their file during the 1–3 years follow-up. Results are expressed as means $\pm$ S.E.M.
Main results
Out of the 88 eligible patients, 74 had at least one body weight reported in their file during the 1–3 years follow-up period and were included in this study. After radioiodine therapy, euthyroidism was achieved in 91.8% patients after 1 year. Pre-treatment median TSH was 0.19 mU/l in grade 1 SCH group and 0.04 mU/l in the grade 2 SCH group ($P<0.01$). Mean follow-up time was 2.47 years and did not significantly differ between the groups ($P=0.352$). Before radioactive iodine treatment, BMI of patients with grade 1 and grade 2 SCH were 27.5 ± 0.9 kg/m^2 and 26.9 ± 0.9 kg/m^2 respectively ($P=0.664$). Post-treatment median TSH levels was similar in both groups. Post radioactive iodine treatment weight gain was

significantly higher in the grade 2 group (2.20 ± 0.73 kg) than in the grade 1 group (0.65 ± 0.39 kg); $P = 0.039$. Increase in BMI was also higher in grade 2 group (1.07 ± 0.27 kg/m^2) than in the grade 1 group (0.26 ± 0.15 kg/m^2); $P = 0.023$. Most of the weight gain was already observed within the first 12 months of follow-up. After radioactive iodine, a significant increase in LDL cholesterol values of 14.3 ± 4.1 mg/dl ($n = 19$, $P = 0.003$) was observed in grade 2 group and not in grade 1 group (10.2 ± 6.9 mg/dl, $n = 19$, $P = 0.157$). A negative correlation was observed between pre-treatment TSH levels and absolute BMI gain ($r = -0.350$; $P = 0.005$). Our study found no significant modifications in glucose after restoration of euthyroidism.

Conclusions

In the follow-up of patients receiving radioiodine therapy for SCH caused by benign nodular goiter, weight gain and raise in serum cholesterol were observed only in the group with SCH grade 2 and not in the group with SCH grade 1. As post treatment TSH values were similar in both groups, this observation is probably related to the severity of the disease before treatment confirming that the distinction between grade 1 and grade 2 SCH is clinically relevant at least for metabolic parameters.

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017

Value of [11C]-methionine PET/CT in preoperative localization of adenomas in primary hyperparathyroidism

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Introduction

The first-line imaging modalities to locate adenomas preoperatively in primary hyperparathyroidism (PHPT) are ultrasonography (US) and subtraction scintigraphy (SuSc). When these contradict each other or are inconclusive an [11C]-methionine PET/CT (MET-PET/CT) or a 4-dimensional computed tomography (4D-CT) can be performed.

Objectives

The aim of this retrospective study was to evaluate the value of MET-PET/CT in the preoperative localization of adenomas in PHPT, especially when US and/or SuSc were inconclusive or negative.

Methods

All patients that underwent parathyroidectomy in the UZ Brussel in the period of 01-01-2008 until 31-12-2017 (10 years) for hyperparathyroidism were selected with exclusion of secondary and tertiary hyperparathyroidism, renal insufficiency (CKD stage 3B or worse), MEN syndrome and known malignancy. Finally, 84 patients were included. The results of US, SuSc, MET-PET/CT and 4D-CT were correlated to intraoperative decline in parathyroid hormone (PTH) levels and to the anatomopathological analysis. Sensitivity and specificity were calculated per-lesion for each imaging modality.

Results

75 patients (89%) had a single parathyroid adenoma and nine patients (11%) had multiglandular PHPT (four patients had two adenomas, and five patients had hyperplasia). Not every patient underwent every imaging modality: 75 (90 adenomas), 62 (75 adenomas), 16 (22 adenomas) and 8 (8 adenomas) patients underwent respectively US, SuSc, MET-PET/CT and 4D-CT. The observed per-lesion sensitivity of US, SuSc, MET-PET/CT and 4D-CT is respectively 40.0%, 32.0%, 59.1% and 62.5%. The observed per-lesion specificity of US, SuSc, MET-PET/CT and 4D-CT is respectively 95.5%, 91.4%, 95.7% and 96.0%. Due to the limited sample size, especially in 4D-CT, the 95%-Clopper Pearson confidence intervals are large and therefore difficult to interpret. A sub-analysis on paired data only between two imaging modalities with a McNemar test showed a significant better per-lesion sensitivity of MET-PET/CT compared to US ($P = 0.039$) and a significant higher per-lesion specificity of US compared to SuSc ($P = 0.035$). The difference in per-lesion sensitivity between MET-PET/CT and SuSc showed a P-value of 0.070. In 70% of the cases where MET-PET/CT was performed after inconclusive or contradicting US and/or SuSc, MET-PET/CT had an additional value in localization of the adenoma.

Conclusion

MET-PET/CT seems a valuable imaging modality in hyperparathyroidism with a higher per-lesion sensitivity than US. Especially when US and/or SuSc are inconclusive or negative, MET-PET/CT directs the surgeon to the correct localization of the adenoma.

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018

Osteoporosis treatment gap in the FRISBEE cohort

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Introduction

Osteoporosis is characterized by a low bone mass and a microarchiterctural disruption. Ageing and estrogen deficiency are the two most important factors for developing osteoporosis. With advanced age the balance between bone formation and resorption becomes progressively negative and non-bone factors contribute to the increased fracture risk with advancing age. Osteoporotic fractures constitute a major cause of morbidity and mortality in the elderly. Post-menopausal fracture risk is more than 40%, accounting for a high morbidity and mortality. Although effective anti-osteoporotic drugs have been available for decades, treatment gap remains at about 80% but the causes of this alarming treatment gap remain poorly understood and are probably multifactorial.

Objectives

The primary objective of our study was to determine the proportion of patients who did not receive a medication to treat osteoporosis after a first validated osteoporotic fracture in a prospective cohort of volunteer post-menopausal women.

Methods

The FRISBEE cohort consists of 3560 post-menopausal women aged 60–85 years at inclusion surveyed yearly for the occurrence of fragility fractures. We examined if a pharmacological treatment was initiated within 2 years after a first radiologically validated fragility fracture occurring during follow-up. We conducted separate analyses for the four classical 'major osteoporotic fractures' (MOFs: vertebra, hip, shoulder/upper arm and wrist), and for 'other major' fractures (ankle, pelvis and sacrum, elbow, knee-except patella, upper- and lower-leg, upper- and lower-arm).

Results

For 386 fractures (285 MOFs and 101 'other major' fractures), the global percentage of untreated women was 84.9%: 82.8% for MOFs (72.5% (29/40) for the hip, 70.5% (67/95) for the vertebra, 91.7% (44/48) for the shoulder, 94.1% (96/102) for the wrist) and 91.1% for the 'other major' fractures.

Conclusion

Our study indicates that the treatment gap in cohort of Belgian subjects who present an osteoporotic fracture has not improved over time and is similar to other population-based studies. More importantly, these data obtained in volunteer women suggest that the main culprit of this therapeutic failure is the doctor and not the patient.

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019

Androgen metabolism during weight loss in men with obesity

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Background

Men with obesity often have low total and, with increasing adiposity, also free testosterone (T) levels, which can partially restore when they lose weight. Although this is in part explained by lower sex-hormone binding globulin (SHBG) production and hypothalamic-pituitary downregulation, it is still not

fully unraveled whether changes in androgen metabolization contribute to this phenomenon.
Aim
Investigating metabolisation of sex steroids during weight loss in men with obesity.
Subjects and methods
Eleven obese men (age 49 ± 10 years, BMI 44.9 ± 5.0 kg/m^2) were recruited prior to adhering dedicated lifestyle changes ($n = 1$) or undergoing gastric bypass surgery ($n = 10$). Before start of weight loss and 3 weeks, 6 weeks, 6 months and 1 year thereafter, 24h urine collections and fasting serum samples were collected. Serum T and estradiol (E2) levels were analyzed using LC-MS/MS and serum SHBG concentrations using immunoassays. Urinary T, 3α-androstanediol, androsterone, 3α-etiocholanediol, etiocholanolone, estrone, E2 and estriol levels were analyzed using gas chromatography coupled to mass spectroscopy. Statistical analyses were performed using linear mixed modelling.
Results
Obese men significantly reduced their BMI through this one-year follow-up study with a mean BMI of 30.3 kg/m^2 after one year ($F(4, 9.173) = 139.105$, $P < 0.001$). Serum T and SHBG concentrations increased by 102% and 87%, respectively (both $P < 0.001$), while serum E2 levels decreased non-significantly ($P = 0.129$). A significant increase of total urinary T concentration was observed during follow-up ($F(4, 29.112) = 4.529$, $P = 0.006$), with a total increase of 101% one year after start of weight loss ($P = 0.001$), while the ratios E2/T and estriol/T decreased ($P = 0.001$ and $P = 0.010$; respectively) suggesting lower relative aromatization. In addition, T metabolisation by 5α-reductase and 3α-hydroxysteroid dehydrogenase (HSD) reflected by 3α-androstanediol/T- and androsterone/T-ratio, decreased during follow-up ($P = 0.006$ and $P = 0.002$; respectively) whereas 3α-etiocholanediol/T-ratio and etiocholanolone/T-ratio, reflecting T metabolisation from the 5β-reductase and 3α-HSD pathway, showed a non-significant decrease ($P = 0.065$ and $P = 0.070$; respectively).
Conclusion
Restoration of T levels into the eugonadal range during weight loss in men with obesity is not only brought about by normalization of circulating SHBG levels but also by increased T production per se as reflected by increased urinary secretion of T. In addition, changes in these men's urinary steroid profile, suggest that alterations in T metabolization also contribute to this. More specifically, besides relatively higher aromatization, higher 5α-reductase and 3α-HSD activity might also play a role in the phenomenon of low T levels in men with obesity.

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020

Uncontrolled gender-affirming hormone use in transgender sex workers in Antwerp

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Background and aims
Research indicates that a significant portion of transgender women are involved in sex work, which is mostly attributed to discrimination of transgender persons on the labour market. Transition-related health risk behaviour, such as uncontrolled hormone use, auto-medication and the use of silicone injections, may lead to several adverse health outcomes for transgender persons. Transgender sex workers are a vulnerable group within the transgender population, who might be at increased risk for these health risk behaviours because of economic marginalisation. However, European research into this topic and risk population remains largely absent. This study is the first exploring these risk behaviours in a European sample of transgender sex workers, as well as the association with their socio-demographic characteristics, their work and their migration pathways.
Methods
This study explores the prevalence of uncontrolled gender-affirming hormone use among transgender sex workers working in window-based sex work in the Antwerp red light district (Belgium), as well as their socio-demographic characteristics and migration pathways. In co-operation with two outreach organizations providing sexual health services to sex workers, a face-to-face survey was carried out among 46 transgender sex workers. Descriptive analyses of this survey sample were supplemented with 9 in-depth interviews with transgender sex workers, which were analysed using Grounded Theory.
Results
The population of transgender sex workers working in the Antwerp' red light district has specific socio-demographic characteristics: they are all assigned male at birth, 83% identifies as female and 76% is from Latin-American descent, mainly from Ecuador. However, a variety of migration pathways is cited, and 30% cites travelling internationally to work, which influences their access to healthcare. Transition-related health risk behaviours are prevalent: current uncontrolled hormone use rate is 32%, and a lot of participants do not follow regular hormone regimens. Engaging in sex work appears to be an important reason for this uncontrolled gender-affirming hormone use and auto-medication, as gender-affirming hormones frequently cause erectile dysfunction and an erection is often required when engaging in transgender sex work.
Conclusions
When addressing this population's health risk behaviour, the specific characteristics of this largely invisible but highly vulnerable population should be taken in account, as well as their work and migration pathways. Access to health care and social services should be ensured, and culturally tailored health interventions that take into account their social context as well as their gender identity should be developed.

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021

Characterisation of testicular function and spermatogenesis in transgender women

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Introduction
If desired, options for gender affirming treatment in transgender individuals may involve gender affirming hormonal therapy. However, the effects on fertility and testicular function are less known. Several studies have been performed with variable results regarding germ cell maturation and testicular function in this population. In order to give correct information to all transgender women, we find it important as a referral center for transgender care, to compare results of earlier studies with our population.
Material and Methods
This prospective cohort study was part of the European Network for the Investigation of Gender Incongruence (ENIGI). Ninety-seven transgender women who initiated gender affirming hormonal therapy (HT) according to the ENIGI protocol and who proceeded with gonadectomy at the Ghent University Hospital, were selected for this substudy. Testicular tissue retrieved during gonadectomy was processed and stained for four different markers. Subsequent immunohistochemical staining was performed for Melanoma-Associated antigen A4 (MAGE-A4), BOLL, CAMP Responsive Element Modulator (CREM), and acrosin. The number of MAGE-A4+ spermatogonia and primary spermatocytes were counted per square millimeter. Healthy controls were used for comparison. Serum levels of sex steroids were measured prior to surgery.
Results
An adequately suppressed testosterone level (< 50 ng/dl) was found in ninety-two percent (89/97) of the participants prior to surgery. The mean time between initiation of HT and surgery was 685 days. In 88% (85/97) of the sections, MAGE-A4 staining was positive. Further immunohistochemical staining could not reveal complete spermatogenesis in any of the participants. There was a positive correlation between serum testosterone levels and number of spermatogonia counted per mm^2.
Conclusion
Gender affirming hormonal therapy with cyproterone acetate plus estrogens leads to complete suppression of spermatogenesis in transgender women. Therefore, it is important to discuss sperm preservation before the start of hormone therapy, as stated in the WPATH guidelines.

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022

Hyperparathyroidism in a patient with sickle cell disease

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An 22-year-old patient with a history of homozygous sickle cell disease (complicated by multiple vaso-occlusive attacks) was referred to the endocrinologist for persistent hypercalcemia for more than one year (between 2.63 and 2.82 mmol/l, N: 2.15–2.50 mmol/l), associated with hypophosphoremia (0.71 mmol/l, N: 0.75–1.39 mmol/l) and elevation of parathyroid hormone (170 ng/l, N <49 ng/l). Cervical ultrasound did not show parathyroid adenoma, but parathyroid MIBI scintigraphy revealed pathological parathyroid tissue at the lower pole of the right lobe compatible with the diagnosis of primary hyperparathyroidism. However, previous blood tests also showed a severe and prolonged deficit of vitamin D (<6 ng/ml, *N*: 30–80 ng/ml) although regular substitution with high doses of Cholecacliferol. Moreover vitamine D deficiency was associated with other fat soluble vitamin (A and E) deficiencies suggesting a malabsorptive pathology. She had around three bowel movements a day but with no clay-colored stool and no diarrhea. The search for antibodies characteristic of celiac disease was negative as well as antibodies against parietal cells and anti-intrinsic factor. A trioleine breath-test confirmed malabsorption with a CO_2 estimated at 3.4% (*N*> 23%). Cholangio-MRI did not show ischemic cholangitis that could be associated with sickle cell disease, but demonstrated a severe atrophy of pancreatic parenchyma that could explain the malabsorption syndrome. Creon was thus prescribed. One year later, she developed inaugural diabetes (polyuria, polydipsia, weight loss with severe hyperglycemia and started insulin therapy with basal-prandial regimen. C-peptide was low but the search for diabetes-related autoantibodies was negative. Regarding the etiology of this pancreatic atrophy, there had no history of acute pancreatitis crisis although they may have gone unnoticed in the context of painful crises associated with vaso-occlusive attacks of sickle cell disease. Pancreatic atrophy due to prolonged hypercalcemia is also unlikely (rare cases described, moderate hypercalcemia and no intrapancreatic calcifications). Given the age of the patient, a genetic origin of chronic pancreatic is being researched. We described the case of a young patient with pancreatic atrophy of unknown origin and secondary exocrine and endocrine pancreatic insufficiencies, with malabsorption syndrome and insulindependent diabetes. Chronic and prolonged vitamin D deficiency induced tertiary hyperparathyroidism with identifiable parathyroid adenoma.

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023

Hypercalcemia as a rare complication of anti-tumor necrosis factor alpha: a case-report and literature study

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Introduction

(Anti-TNF-α) therapy is widely used for the treatment of inflammatory diseases. The most frequent adverse events induced by anti-TNF-α therapy are infections and malignancies. However, reports of paradoxical sarcoidosis-like reactions are on the rise in patients receiving anti-TNF-α.

Clinical case

A 61-year old woman, with a medical history of sero-positive rheumatoid arthritis on Adalimumab treatment (anti-TNF-α), was referred to our outpatient clinic by her general practioner for a non-parathyroid hormone (PTH) driven hypercalcemia. Her calcium and PTH concentrations were respectively reported as 2.65 mmol/l and 3.0 ng/l. Additional testing confirmed low PTH with a normal 25-hydroxyvitamin D but an elevated 1,25-dihydroxyvitamin D (Table 1). PET-CT revealed bilateral hilar and mediastinal lymphadenopathy suggestive of tuberculosis (TBC), lymphoma or sarcoidosis. A negative interferon gamma release assay, acid-fast bacilli (AFB) and Ziehl stain excluded TBC. A percutaneous lung biopsy unveiled non-necrotizing granulomas with no discernible microorganisms by Gramm stain and Grocott's methenamine silver. Thus, the diagnosis of a Adalimumab induced sarcoidosis – like granulomatosis was made. To date we have identified 110 known cases of sarcoidosis-like lesions induced by TNF-α inhibitors, of which only eight cases reported hypercalcemia. Hereof, three were accompied by acute kidney injury[(1–3)].

Table 1 Laboratory results AZ Sint Jan

Laboratory test	Results	Reference value
Calcium	2.60 mmol/l	2.2–2.55 mmol/l
Phosphorous	1.18 mmol/l	0.81–1.45 mmol/l
Albumin	40.4 g/l	39–54 g/l
PTH	2.0 ng/l	15–65 ng/l
25-hydroxyvitamin D	24.4 ng/ml	20–30 ng/ml
1,25-dihydroxyvitamin D	133.1 ng/l	20–80 ng/l
Creatinine	0.78 mg/dl	0.51–0.95 mg/dl
24h calciuria	12.2 mmol/24u	2.5–7.5 mmol/24u

Conclusion

1,25-dihydroxyvitamin D induced hypercalcemia is a rare or underreported complication of anti-TNF-α therapy. An extensive work-up with exclusion of TBC and lymphoma is indicated. Although reports of sarcoidosis-like granulomatosis as a complication of anti-TNF-α are increasingly common, it remains a rare complication (1/2800). Nevertheless, it has to be included in the differential diagnosis of a 1,25-dihydroxyvitamin D induced hypercalcemia. In most cases, discontinuation of anti-TNF leads to recovery[(4,5)].

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024

A case of meningioma after cyproterone acetate use

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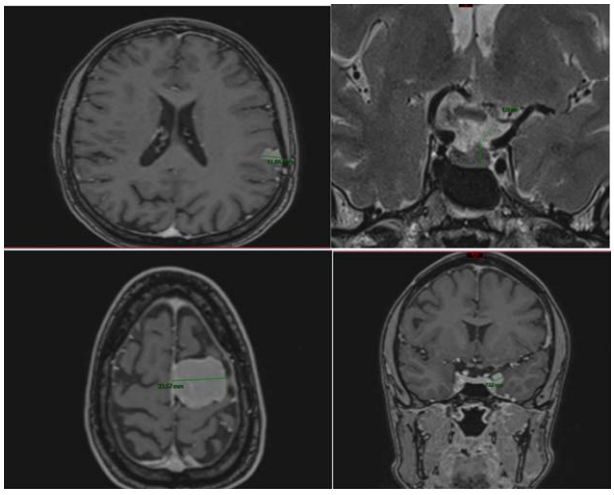
A 43-year-old roman, previously living in France was referred to the endocrinology department for Hashimoto's hypothyroidism in 2017. Thyroid function was easily normalized by a treatment by thyroxine. She had also a medical history of severe alopecia since the age of 20. The diagnosis of androgenetic alopecia was made at that time by a French dermatologist and treatment by estradiol valerate 2 mg with cyproterone acetate (CPA) 50 mg was started. The dose of CPA was lowered to 25 mg 10 years later, in association with finasteride 5 mg, minoxidil 5% and an oral contraceptive pill (ethynilestradiol 0.02 mg and drospirenone 3 mg). In December 2018, she reported atypical headaches concomitantly with a stress episode. She had also a slight elevation of the prolactin level. Despite the atypical nature of headaches, a brain MRI was proposed in view of the prolactin level and the recent concerns about the risk of meningioma in patients with a long term treatment by CPA. Brain MRI was performed, revealing incidental discovery of 4 meningiomas in the left cerebral hemisphere. (34 mm, 19 mm, 13 mm and 7 mm). CPA and oral contraceptive pill were stopped. The brain surgeon confirmed the lack of indication for immediate surgery. In order to evaluate the evolution of the lesions after stopping anti-androgenic treatment a control brain MRI is scheduled for October 2019. Meningiomas are benign tumors, with a clear female predominance, arising from the meningothelial cells of the arachnoid membrane (20% of the intracranial

tumors). Progesterone receptor responsiveness to sex hormones has been hypothesized to promote the development of meningioma. The relationship between meningiomas and CPA is now well documented. CPA is a progestin-like drug with a strong anti-androgenic effect, used to treat androgen-related alopecia in women, but also, at higher doses, inoperable prostate carcinoma and transgender women (male to female). Risk of meningioma among users of CPA was evaluated in three cohort studies.[1,2,3] A retrospective cohort study performed in Spain demonstrated that patients (70% female, 30% male) using high dose of CPA (50 mg or more) had an incidence rate of 60/10000 person-years (6.6 person/10000 -years in the control group), with a rate ratio of 11.4 after adjusting for age and gender. Among the low dose CPA users, no meningioma was identified.[1] Risk of meningioma was also significantly higher in a study cohort performed in the Netherlands, evaluating occurrence of brain tumors in adult transwomen (male to female) taking cross-sex treatment consisting of high dose CPA (50–100 mg). The median person-time of observation was 6.22 years. Standardized incidence ratio (SIR's) of meningiomas were 4.1 compared with the incidence rate of a European female population and 11.9 compared with an European male population.[2] Finally, a UK cohort study (1996–2008) found out a significant increased risk of meningioma among male current users of high-dose CPA (>50 mg) compared with no-users (Odds-ratio of 6.30). No significantly increased risk was found among past users (most recent prescription ended more than 1 year before index date) or among low dose CPA users.[3] Evolution of meningiomas after stopping CPA was evaluated by a French series of 12 patients taking CPA for a long period (8–30 years) at an average dose of 40 mg. After stopping CPA, tumor shrinkage was observed in 11 out of 12 cases within a mean period of 5 months and there was no regrowth of the tumor in any cases during a mean 12-month follow up, which confirms that medication withdrawal followed by observation is the first line of treatment.[5] There a no clear recommendations on the follow up needed in patients treated by CPA. A review on the safety of CPA is presently being carried out by the EMA. As CPA is mainly prescribed in France, the only recommendations presently available for the follow up are those of the "agence nationale de sécurité du médicament" based on very limited data:

- Prolonged use of CPA at high dosage should be avoided if possible (risk of meningioma multiplied by 7 for a 6-month treatment and by 20 for a 5-year treatment at a dose > 50 mg);
- MRI should be performed at the beginning of treatment for all patients;
- In case of continuation of treatment, MRI will be renewed at 5 years then every 2 years if the MRI at 5 years is normal;
- In patients who have stopped treatment, it is not necessary to perform brain imaging in the absence of clinical signs;
- If meningioma is found, the treatment must be stopped permanently. Neurosurgical advice is recommended – conservative treatment is often possible as meningiomas are regressing or stabilizing after stopping treatment;
- The need for treatment by CPA must be reassessed for each patient;



In conclusion, we report the case of a 43-year-old woman with multiple meningiomas occurring after a 23-year-treatment with high dose of CPA prescribed for androgenetic alopecia. Treatment was stopped and we adopted a conservative attitude with a follow-up brain MRI scheduled on October 17th 2019…

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025

A rare cause of central diabetes insipidus

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Case

A 42-year old woman was referred to the endocrinology department for polydipsia and polyuria of sudden onset one month prior to presentation. She drank between 8 and 10 litres of water per day and complained of thirst, asthenia and lighter menstruation under her usual oral contraceptive pill. In addition to contraception she took 50 µg of L-thyroxine for Hashimoto thyroïditis. She had also a medical history of pink-red cutaneous lesions evolving for more than 10 years, first appeared in the axillae. The initial skin biopsy evoked granuloma secondary to aluminium contact but eviction of deodorant did not improve the existing lesions and other granuloma appeared in the sub mammary and inguinal folds. More recent biopsies retained the diagnosis of multiple reticulo-histiocytomas. Systemic involvement was excluded for 5 years by annual bone scintigraphy, chest and abdomen CT. Considering the polyuria-polydipsia syndrome associated with hypernatremia, independently of any deshydratation test (Na 146 mmol/L; N 135–145 mmol/l), diagnosis of central diabetes insipidus was made and patient received DDAVP nasal spray therapy. It allowed rapid improvement of the symptoms and normalization of natremia. Diagnosis was confirmed by a magnetic resonance imaging (MRI) that showed loss of normal hyper intense T1-weighted signal of the posterior pituitary gland, but also thickening of the pituitary stalk and lesion of the right side of the gland mimicking micro adenoma (7*9*9 mm). At this time circulating levels of anterior pituitary hormones were normal, except for mild hyperprolactinemia (PRL 704 µUI/ml; $N<500$). Gonadal and adrenal axes were difficult to interpret because of the contraceptive pill. After stopping this treatment, patient became amenorrheic and hormonal profile demonstrated hypogonadotropic hypogonadism. Considering the neuroendocrine manifestations, new cutaneous biopsies were performed, revealing CD68+, CD163+S100 CD1a -, CD207-, ALK- histiocytes evoking non-Langerhans histiocytosis (NLH). No BRAF or NRAS mutation was found. The diagnosis of Erdheim-Chester disease (ECD) or xanthoma disseminatum (XD) was thus evoked. Several weeks later, patient complained of polyarthralgia (painful knees and shoulders) and back pain irradiating in both legs. Bone scintigraphy and knee X-rays did not show any lesion. 18F-FDG-PET/CT revealed focal L3 vertebra hypermetabolic lesion and MRI confirmed infiltration of L3 but also to a lesser degree of L5. Biopsy of the L3 vertebral bone confirmed, as for cutaneous biopsy, NLH. Radiological follow-up showed spontaneous regression of pituitary infiltration with persistent thickened stalk, and new small non-hypermetabolic lesions in D12 and L1vertebra. Excepted DDAVP nasal spray, L-thyroxine and oestro-progestogenic substitutions, expectant observation was proposed as the patient was poorly symptomatic and systemic treatment available being heavy and often disappointing.

Discussion

Histiocytoses are rare disorders characterized by the accumulation of dendritic cells, macrophages or monocyte-derived cells in various tissues. These can affect children and adults and be uni- or multifocal, mild or disseminated. NLH distinguishes from Langerhans cell histiocytosis (LCH) by the absence of positivity of CD1a marker on histiocytes.[1,2] LCH and NLH may affect any organ of the body including skin, bones and pituitary gland.[2,3] NLH include a broad spectrum of pathologies including Erdheim-Chester disease (ECD) characterized by bilateral, symmetric cortical osteosclerosis of the diaphyseal and metaphyseal regions in more than 95% of cases[1,2,4], and xanthoma disseminatum (XD)

characterized by predominant mucosal and skin involvement.[1,2] Diabetes insipidus can occur in LCH as in NLH and in ECD as in XD. Furthermore, more than 50% of the ECD patients exhibit BRAF-V600E mutation like in LCH supposing a common cellular origin.[1] Differential diagnosis between these different forms of histiocytoses is thus very difficult.

Conclusion

We described the case of a 42-year old woman with histopathologic features of NLH. She had cutaneous eruption and diabetes insipidus compatible with the diagnosis of XD. Female gender and bone involvement rather suggest ECD, but the absence of BRAF mutation and the non-typical bone lesion argue against. Finally, we described a rare cause of diabetes insipidus resulting from indeterminate (between XD and ECD) NLH with pituitary and vertebral involvement.

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026

An adrenal tumor with gynecomastia

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Initial presentation and work-up

A 42-year-old man was referred to the endocrinologist because of an incidentaloma of the right adrenal with a maximum diameter of 4.2 cm on echography of the abdomen. Echography was performed because the patient presented with icterus. An abdominal CT scan confirmed a right adrenal mass with a maximum diameter of 5.1 cm. The intensity of the adrenal adenoma amounted 39 Hounsfield units. The patient did not have a significant medical history, especially no arterial hypertension. He did not use any medication. The patient did not have palpitations, headaches or sweat attacks. The last 3 months he lost 5 kg of weight which he attributed to stress and diet. He did not have spontaneous ecchymosis, colored striae or tiredness. He spontaneously complained about bilateral breast development since 5 months. His libido was normal and he did not have erection problems. Clinical examination showed a normal blood pressure and no Cushingoid stigmata. Bilateral gynecomastia was notified, which was confirmed on echo-mammography. Screening for hormonal activity of the incidentaloma showed no arguments for primary hyperaldosteronism, autonomous hypercortisolism or phaeochromocytoma. DHEAS was normal (278 μg/dl). Blood tests performed because of the bilateral gynecomastia showed a hypogonadotropic hypogonadism and a slightly elevated oestradiol of 44 ng/l. Prolactin level was normal. Hyperthyroidism, liver disease, testicular tumors and renal disease were excluded. Further examination by MRI of the adrenal glands did not show pronounced hypervascularization of the mass. A PET/CT scan showed a mild heterogeneous tracer capitation of the adrenal mass and did not show enlarged retroperitoneal gland complexes or distant metastases. Since the incidentaloma of the right adrenal was larger than 4 cm, the patient was referred to the endocrine surgeon to perform a right adrenalectomy.

Diagnosis and treatment

Histological examination of the right adrenal showed a completely resected adrenocortical carcinoma (ACC) (the tumor satisfied 4 of 9 items in the Weiss criteria) with a diameter of 2.8 cm with growth in the adrenal capsule and surrounding fatty tissue. TNM showed a pT3L0V0Pn0R0 classification. Due to growth in the surrounding tissue we diagnosed a stage 3 ACC based on the ENSAT (European Network for the Study of Adrenal Tumor) classification. Decision to start adjuvant treatment with mitotane was made during a multidisciplinary consultation. Patient mentioned disappearance of gynecomastia 2 weeks after surgery which was confirmed by clinical examination. Laboratory tests showed a decline in oestradiol level form 44 ng/l pre-operative to 9 ng/l postoperative and an almost complete recovery of the gonadotropic axis. DHEAS post-operatively was 125 μg/dl. Final diagnosis of an estrogen-producing ACC was made.

Discussion

ACC stays a rare endocrine malignancy with estrogen-producing feminizing ACC being even more rare with an incidence of 2% among all adrenocortical carcinomas[1]. They are mainly observed in men and children[2]. A normal adrenal gland has little aromatase activity. Oncogenesis leads to aromatase expression and induces estrogen synthesis. Excessive transformation of androgens to estrogens leads to an increase in estrogens/androgens ratio responsible for gynecomastia and other hypogonadism features and an inhibition of the hypothalamic-pituitary-gonadal axis causing a lack of luteinizing hormone-releasing hormone pulsatility inducing a low luteinizing hormone and follicle-stimulating hormone secretion[1,2,3,4]. The management of estrogen-producing ACC is similar to the management of other adrenal tumors. The guidelines of ENSAT conclude to give mitotane as adjuvant treatment to patients with high risk of recurrence (stage 3, R1 resection, or Ki67 $>10\%$)[5]. In case of incomplete resection of estrogen-producing ACC, aminoglutethimide can be used as a complementary treatment. It blocks cortisol, aldosterone and androgens synthesis and also inhibits peripheral aromatization of androgens to estrogens[2,5].

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Catastrophic antiphospholipid syndrome with bilateral adrenal hemorrhage: a case report

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Background

Adrenal insufficiency is a rare but potentially life threatening complication of the antiphospholipid antibody syndrome (APS). The adrenal gland is the most commonly involved endocrine organ with adrenal insufficiency reported in 0.4% of APS cases. Adrenal failure more often follows other thromboembolic manifestations of APS.

Case report

We report a 25-year-old male with systemic lupus erythematosus (SLE) with antiphospholipid syndrome (triple positive antiphospholipid antibody profile, complicated by subtotal amputation of the left lower leg), who presented to the emergency department for a hemorrhagic shock caused by a massive hematoma of his right leg following a trauma. His maintenance therapy included low dose methylprednisolone, mycophenolate mofetil, hydroxychloroquine, acenocoumarol and acetylsalicylic acid. At presentation, he was severely anemic (hemoglobin 5.6 g/dl) and the INR value was 4.9. He received transfusion of blood products and his anticoagulant therapy with acenocoumarol was suspended and replaced by LMWH. During his hospitalization, he began to complain of left iliac fossa pain. He was afebrile and had a normal blood pressure without tachycardia. Echography of the abdomen showed free fluid, both perihepatic-splenic and in the pelvis. A CT scan of the abdomen demonstrated wall thickening of the sigmoid colon. Sigmoidoscopy was performed which demonstrated a mild ischemic colitis, insufficient to explain the patient's symptoms as his condition deteriorated over the following days with the development of a paralytic ileus and mild jaundice. His laboratory values were as follows: CRP 299 mg/l, LDH 873 U/l, ALP 162 U/l, GGT 181 U/l, bilirubin 3.78 mg/dl (direct 1.6); platelet count 85×10^3 per mm^3, hemoglobin 11.4 g/dL and white cell count 21.6×10^3

per mm^3 with 82.1% neutrophils. A repeat CT scan of the abdomen showed a hydrops of the gall bladder with cholecystolithiasis, without signs of cholecystitis, but with the unexpected presence of an infrarenal aortitis. Endoscopic ultrasonography demonstrated hemobilia both in the extrahepatic bile ducts as in the gall bladder (despite the negative CT scan), for which endoscopic ultrasound-gallbladder drainage and ERCP with endoscopic pancreatic sphincterotomy and positioning of a duodenobiliary stent were performed. Broad-spectrum antibiotics were started. Two days later, the CT scan of the abdomen displayed a bilateral adrenal hemorrhage, not previously present. All of the patients's problems were finally explained by the diagnosis of a catastrophic antiphospholipid syndrome (CAPS). Subsequently, the patient responded promptly to a course of high dose intravenous corticosteroids and plasmapheresis.

Discussion

The present case report describes a patient with a CAPS due to the occurrence of different thrombotic and bleeding events, including bilateral adrenal hemorrhage. The catastrophic APS is a rare variant of APS characterized by micro- and/or macrothrombi in multiple organs. It is commonly triggered by several factors including infection, trauma, surgery or the withdrawal of oral anticoagulation. Our patient had a traumatic event, necessitating the interruption of his oral anticoagulation therapy that probably triggered CAPS. Moreover, he was triple positive for antiphospholipid antibodies, a well-recognized additional risk factor. Although bleeding is exceptional, both thrombotic and hemorrhagic manifestations can occur concomitantly in CAPS. Hemorrhagic diathesis may be due to the occurrence of micro-thrombotic events, severe thrombocytopenia, hypoprothrombinemia and /or acquired von Willebrand's syndrome. The occurrence of hepatobiliary bleeding and bilateral adrenal hemorrhage, as described in this case, is exceptional. Futhermore, the diagnosis was difficult as the patient did not present with classical Addison's crisis as he was treated with methylprednisolone for SLE.

Conclusion

We describe a patient with SLE and triple positive antiphospholipid syndrome, who developed a CAPS, with ischemic colitis, hemorrhagic cholangitis, infrarenal aortitis and bilateral adrenal hemorrhage. Adrenal hemorrhage is a rare but severe complication of APS. Clinicians should be aware, especially in patients with known APS.

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A cherry-tomato like thyroid

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Context

A lingual thyroid is a relatively rare clinical entity. It is the most common subtype of ectopic thyroid. An ectopic thyroid is caused by an aberrant descent of the thyroid gland from the foramen caecum to its normal pretracheal position during embryogenesis. A lingual thyroid is located at the midline of the tongue base. It can be asymptomatic, but it may also cause dysphagia, upper airway obstruction, haemorrhage or dysphonia. Moreover, about 70% of patients with lingual thyroid have hypothyroidism.

Case report

A 29-year-old female patient was referred for mild primary hypothyroidism (TSH 9.96 mU/l and FT4 0.86 ng/dl). She was asymptomatic and had no medical history. As there were no biochemical signs of auto-immunity, an ultrasonography was performed in search of an hypoechoic hypervascular thyroid. This revealed the absence of any visible thyroid gland tissue, raising the suspicion of an ectopic thyroid. A Tc-99 SPECT-CT was performed and revealed a lingual thyroid (uptake at the base of the tongue and no thyroid bed uptake; and a visible mass on CT). Laryngoscopy confirmed a spherical mass (3 cm in diameter) at the midline of the tongue base (Figure 1A). No mucosal lesions could be seen. The vocal cord mobility was symmetrical.

Levothyroxine treatment was initiated to treat the hypothyroidism and to prevent further growth of the lingual thyroid, aiming at a TSH 0.3–2 mU/l. No surgical intervention was planned since the patient did not suffer from dysphagia or dyspnoea.

Laryngoscopic re-evaluation after 2 years of treatment with levothyroxine showed stable dimensions of the lingual thyroid. However, after 7 years of treatment, the size of the lingual thyroid was significantly smaller (2 cm) (Figure 1B).

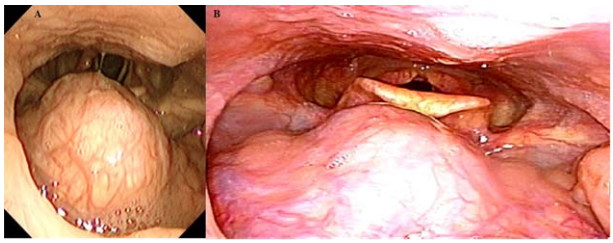

Figure 1 Laryngoscopic follow-up of the lingual thyroid gland. (A) At diagnosis. (B) After 7 years of treatment.

Conclusion

Observation and levothyroxine treatment aiming at a low normal TSH was effective and may be a good alternative to surgery in a- or oligosymptomatic patients with lingual thyroid.

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ACTH-dependent hypercortisolism: always follow your nose

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A 41-year-old woman presented with a puffy face since five months. She experienced alopecia, hirsutism, easy bruisability, amenorrhea and proximal muscle weakness. Clinical examination revealed a moonface, centripetal obesity, proximal muscle atrophy, thinned scalp hair, hyperpigmentation in sun-exposed neck region, ecchymosis and arterial hypertension grade 1. Blood analysis showed elevated morning cortisol, elevated morning ACTH of 66.1 pg/ml (normal 10–60), hypokalemic metabolic alkalosis (potassium 2.6 mmol/l, bicarbonate 34 mmol/l) and hypernatremia (149 mmol/l). Cushing's syndrome was diagnosed with elevated 24-hours urinary cortisol excretion of 963 µg/24 hours (normal 21-292) and elevated late-night salivary cortisol of 0.437 µg/dl (normal <0.107). Loss of circadian rhythm and high ACTH and cortisol values at midnight confirmed ACTH dependency. No adenoma could be visualised on MRI of the pituitary gland. Inferior petrosal sinus sampling (IPSS) displayed a central-to-peripheral ACTH gradient of 2.8: clearly above the cut-off of 2.0. Surprisingly, we did not observe the expected rise in ACTH gradient after CRH-stimulation, with a gradient below 3.0 (1.4 after 5 minutes and 1.2 after 10 minutes). Additional PET-CT showed intense metabolic activity in the left anterior ethmoidal sinus and left upper nasal turbinate, extending to the middle and lower left nasal cavity. Biopsy of this polypoid lesion revealed an olfactory neuroblastoma (ONB) with positive immunostaining for ACTH. Our patient underwent endoscopic resection of the tumour as far as the lamina cribrosa, including resection of the entire middle turbinate. The exposed dura mater and the nasal septum showed no signs of tumour invasion. Postoperative values of cortisol and ACTH were undetectable, suggestive of successful resection. Anatomopathological analysis confirmed our previous diagnosis. Olfactory neuroblastoma (syn. esthesioneuroblastoma) is a rare neoplasm originating from neuroectodermal olfactory cells situated in the upper nasal cavity, representing about 3% of all sinonasal malignancies. Typical clinical features include unilateral nasal congestion, recurrent epistaxis, sinusitis, headache and anosmia[1,2]. ONB

presenting with ectopic ACTH syndrome (EAS) is extremely rare. To our knowledge, only 21 cases have been published. IPSS is considered to be the most reliable test to distinguish Cushing's disease from ectopic ACTH secretion, however, subsequent studies showed that diagnostic accuracy is not always 100%[3,4]. False negatives occur in 10–15% of patients. First, sampling errors occur due to technical difficulty of the procedure or anatomical variations of the petrosal sinus venous system[3]. Second, patients must be in a hypercortisolemic state at the time of the IPSS procedure, warranting suppression of endogenic pituitary corticotrophs[5]. Therefore, medical treatment to control hypercortisolism must be stopped well in advance[3,5]. Thirdly, due to variable ACTH secretion, a positive central-to-peripheral gradient may not be reached at time of IPSS. False positive results are less frequently seen. One explanation is tumour localization adjacent to the upstream of pituitary venous drainage, as in our case[4]. Clinicians should be aware that inconsistent IPSS results might be due to an ACTH-producing tumour in the sinonasal region. In case of EAS, especially with inconsistent IPSS results, one should always follow one's nose and look at the sinonasal region.

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A sarcoidosis-lymphoma syndrome revealed by hypopituitarism

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Introduction

Sarcoidosis is a systemic disease of unknown aetiology, characterized by non-caseified granulomatous reaction that can involve multiple organs. The disease typically presents with pulmonary infiltrates, bilateral hilar and mediastinal lymphadenopathy and uveitis, but may also less frequently affect other organs, including the hypothalamic-pituitary axis. Malignancy rates in sarcoidosis patients have been reported as 1 to 2%[1,2], chronic inflammation being a risk factor. The risk of hematologic malignancy is especially higher among these patients, so that the existence of a specific sarcoidosis-lymphoma syndrome has been suggested. We report here for the first time the co-occurrence of Hodgkin's lymphoma (HL) and proven pituitary sarcoidosis.

Case report

A 26-year-old woman presented with recent headache and fatigue. Biological investigations disclosed an inflammatory syndrome (CRP 57.3 mg/l; normal range (NR) $<$5.0 mg/l), mild hypercalcemia (2.60 mmol/l; NR: 2.15–2.50) with low PTH (19 pg/ml; NR 15–80) and complete anterior hypopituitarism. A magnetic resonance imaging (MRI) of the pituitary gland was therefore performed and revealed a symmetric enlargement with a heterogeneous signal. Ophthalmological examination showed an asymptomatic bilateral anterior and posterior uveitis. A puncture of the anterior chamber was also performed for measurements of IL-10 concentration which was low (1.01 pg/ml) and IL-6 concentration which was high (200 pg/ml). This low IL-10/IL-6 ratio was more consistent with uveitis of non-neoplastic etiology. A diagnosis of pituitary sarcoidosis was suspected.

A 18-FDG-PET fused with total body CT scan was performed and showed large hypermetabolic left unilateral hilar and mediastinal lymphadenopathies, left supraclavicular and axillar adenopathies, and an enhanced signal in the pituitary gland. As the localization of lymphadenopathies was not evoking a sarcoidosis in first instance, an excisional biopsy of a left supraclavicular adenopathy was performed showing classic nodular sclerosis Hodgkin's lymphoma (HL). A diagnostic transsphenoidal biopsy of the pituitary gland was proposed for accurate staging of the HL and surprisingly revealed typical granulomatous inflammation secondary to sarcoidosis, leading to the final diagnosis of a *sarcoidosis-lymphoma syndrome*.

Discussion

A diagnosis of systemic sarcoidosis was first considered in our patient, based of low PTH-hypercalcemia, bilateral uveitis of non-neoplastic origin, a pituitary inflammatory mass at MRI with complete anterior hypopituitarism (which was the initial manifestation) and hilar lymphadenopathies detected on FDG PET/CT. However, the localization and asymmetry of lymphadenopathies was not fully typical of sarcoidosis. Excisional biopsy of a left supraclavicular adenopathy was therefore performed to exclude another diagnosis and indeed showed typical pathological features of nodular sclerosis HL.

As involvement of the CNS is very uncommon in HL, any lesion in the brain of a patient known for HL should be investigated by biopsy for adequate staging and to rule out a second disease process[3]. In our patient, the pituitary biopsy indeed revealed a second diagnosis of sarcoidosis. Such association of sarcoidosis and lymphoproliferative disease has previously been reported as the *sarcoidosis-lymphoma syndrome*. Both diseases may be detected simultaneously, but usually lymphoma occurs after sarcoidosis with a median interval of 24 months[4]. However, the development of sarcoidosis in patients with lymphoma has been also reported[5]. The pathogenesis of this association may be explained by the inflammatory response in sarcoidosis increasing mitotic activity in lymphocytes and the greater risk of lymphocytes undergoing mutations, or by some common immunological abnormalities seen in both disorders In any case, the co-existence of sarcoidosis and lymphoma at first evaluation constituted a real diagnostic challenge.

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A novel pathogenic mutation in neurofibromatosis type 1

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Introduction

Neurofibromatosis type 1 (NF1) is one of the most frequent genetic dominant syndrom in men with a prevalence of 1 in 2600 to 3000 individuals worldwide. NIH NF1 diagnostic criteria are driven by the most frequent manifestations of the disease (café au lait macules (CAL), neurofibromas, freckling, optic glioma, Lisch nodules and osseus lesions). There are many clinical manifestations of NF1 (neurological, cardiovascular, gastrointestinal, endocrine and orthopedic features). Phechromocytoma is one of them, occurring in approximately 0.7% of cases.

The protein encoded by NF1 gene, neurofibromin, is a RAS GTPase-activating protein. NF1 belongs to the group of RASopathies which are syndromes predisposing to benign and malignant tumors. There are more than 1400 indentified mutations of NF1 gene of which 50% are singular mutation. NF1 is sporadic in approximately 50% of the cases. The penetrance is complete but there is a lack of genotype-phenotype correlation, except in some cases, probably because of the existence of modifier genes.

Case report

We report the case of a 23-year-old men who complained for recent discomfort characterized by paroxysmal headache, palpitations with unusual fatigue, epistaxis and severe hypertension. He didn't take any medication or drug. He had no medical history except the removal of an unsightly frontal skin lesion. Clinical examination showed CAL spots and a lesion suspected of neurofibroma on the right forearm. Repeated 24-hours urine fractionated metanephrines and catecholamines measurements showed elevation of catecholamines and (nor) metanephrines level between 7- and 10-fold the upper limit of reference range.

Abdominal CT revealed a voluminous mass of 50×30 mm with a high density (+40 HU without contrast) in the left adrenal gland. After adequate preparation, patient underwent left adrenalectomy and excision of the forearm lesion. Histopathology confirmed the suspected diagnosis of pheochromocytoma and neurofibromatosis. A genetic testing to search a NF1 mutation has been performed and revealed an heterozigoty for the variant c.5791T>A(p.TRP1931Arg). No other genetic variant was identified with cDNA sequencing and MLPA. This variant had previously been reported in a adult man with CAL spots and freckling but without neurofibromas. In the LOVD database this variant is reported as a variant of unknown clinical significance. We decided to perform segragation analysis within his family in ordrer to reveal wether this variant is present in the unaffected parents. Target mutation analysis showed the absence of the tested NF1 variant in both parents of the patient, revealing a de novo event in the patient and a new deleterious effect of the NF1 variant c.5791T>A(p.TRP1931Arg).

Conclusion

We report a novel pathogenic mutation responsible for pheochromocytoma.

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Peptide receptor radionuclide therapy controls inappropriate calcitriol secretion in a pancreatic neuro-endocrine tumor

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A 57 years-old patient presented with back pain, general discomfort, polydipsia, polyuria, fatigue and recent weight loss of 10 kg. Biochemical evaluation showed hypercalcemia (2.85 mmol/l; normal: 2.15–2.55) with low PTH level (14,2 ng/L; normal 14.9–56.9 ng/l) excluding primary hyperparathyroidism. The most frequent cause of hypercalcemia with non-elevated PTH levels is an underlying malignancy[1]. CT-thorax-abdomen showed a pancreatic neuroendocrine tumor (pNET) with multifocal liver metastases, Ki-67 index 15 to 20% (grade 2). Up to 80% of hypercalcemia of malignancy (HCM) are caused by systemic secretion of PTH-related Peptide (PTHrP)[2]. PTH and PTHrP increase kidney calcium reabsorption and stimulate the maturation of osteoclast precursors, increasing bone resorption[3]. However, the PTHrP value was normal ($\leq$ 20.0 pg/ml). Osteolysis mediated by local tumor cell secretion of osteoclast activating cytokines accounts for 20% of the cases of HCM[1]. Although our patient had some osteodense skeletal metastases, these bone lesions alone could not explain his marked hypercalcemia. A rare entity (<1%) of HCM is excessive production of calcitriol due to overexpression of 1α-hydroxylase by the tumor cells. This causes ectopic conversion of 25-hydrovitamine D to calcitriol, leading to increased intestinal and bone resorption of calcium[4]. Patient's calcitriol levels were markedly increased up to 134.3 ng/l (normal: 20.0–80.0), confirming the cause of hypercalcemia. The well-known somatostatin receptor (SSTR) expression in NETs is the foundation of the use of 'cold' (i.e. non-radioactive) somatostatin analogs (SSAs) as a pharmacological treatment. Although initial treatment with the SSA lanreotide 120 mg 1 ×/month and everolimus resulted in stable morphological disease, there was no improvement of the hypercalcemia nor of the associated symptoms. Another strategy exploiting SSTR overexpression are radiolabeled SSAs, for example labeling the peptide vector DOTA-Tyr3-octreotate (DOTATATE) which has high affinity for SSTR2. Due to the specific decay characteristics of the radionuclides, the radiopharmaceutical can be used for diagnostic purposes (molecular imaging by use of gallium68, e.g.) or therapeutic purposes (Peptide Receptor Radionuclide Therapy (PRRT) by use of lutetium-177, e.g.). Currently, PRRT by means of radiolabeled SSAs represents an established, evidence-based treatment modality in case of inoperable/metastatic well-differentiated GEP-NETs4 and its role has been proven by the excellent results obtained in the randomized, controlled NETTER-1 trial[5]. Based on these data the patient was referred for evaluation the possibility of PRRT with 177Lu-DOTATATE and in the meantime FOLFOX bridging therapy was started. The 68Ga-DOTATATE scan revealed intense SSTR expression in the pancreatic lesion as well as strong uptake in the multifocal liver metastases and the skeletal metastases. All malignant lesions had an uptake intensity above the spleen (Krenning score grade 4). The 18F-FDG-PET/CT showed an intense hypermetabolism in some of the liver metastases (metabolic grade 3). There were no mismatch lesions (18F-FDG+/SSR−). Evaluation of the renal function showed no contraindication for therapy. Based on this satisfying work-up, four cycles of PRRT were given, with a treatment interval of 8 weeks up to a cumulative activity of 29.6 GBq. Clinical and biochemical follow-up after each therapy showed no major side effects. Three months after the final cycle there was a marked decrease in serum calcium levels up to normal values as well as a resolution of the associated symptoms. Although there was a clear morphologic response, some liver lesions expressed an increase in 18F-FDG uptake compared to baseline suggesting metabolic progression. The patient was started with temozolomide-capecitabine with good tolerance and continuing morphological and biochemical disease stabilization with normal serum calcium levels as well as normal calcitriol values was observed. This case highlights the role of nuclear medicine in patients with hypercalcemia and documents for the first time the potential of PRRT to control inappropriate tumoral secretion of calcitriol, as has been shown with other hormones secreted by NETs.

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A rare double cause of primary hyperparathyroidism

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Case

A 56-year-old patient was referred to our endocrinology unit for management of severe hypercalcemia. He had complained initially from asthenia, intractable nausea and vomiting and weight loss (10 kg), but now also suffered from polyuria-polydipsia, bradypsychia and bradylalia, and diffuse joint pain with loss of strength in the lower limbs. Initial laboratory investigations showed a parathyroid crisis with marked increases of parathyroid hormone (PTH) at 2138.5 pg/ml (45×ULN), calcemia at 4.75 mmol/l (2.10–2.55), and urinary calcium excretion at 714 mg/24 h. The patient had severe acute renal failure (AKIN 3), nephrolithiasis, and osteoporosis, with a fracture of the radial pallet occurring 8 weeks before admission.

Further investigations revealed a 6 cm right para-mediastinal mass responsible for a left tracheal deviation on chest X-ray. This was confirmed by cervical ultrasound and cervico-thoracic CT which showed a predominantly cystic mediastinal mass with no evidence of parathyroid adenoma in orthotopic position. There was also a goiter with multiple non-suspect infracentimetric nodules. The parathyroid scintigraphy showed intense uptake of MIBI in the antero-superior portion of the mass, corresponding to the solid part, without other uptake. Given the persistence of severe hypercalcemia after treatment by intravenous hydration and furosemide, the patient received a pamidronate infusion leading to a rapid reduction in serum calcium to 2.6 mmol/l 24 hours before *en-bloc* resection of the mass by sternotomy. Pathological analysis revealed a parathyroid carcinoma with apparent R0 resection.

In the early postoperative period, the occurrence of a hungry bone syndrome required massive calcium and vitamin D substitution, which was progressively reduced and withdrawn 10 months postoperatively. After 2 years, hypercalcemia progressively recurred (from 2.56 to 2.83 mmol/l) with PTH remaining in the normal range. A relapse or extension of the parathyroid carcinoma was first suspected.
However, a new cervico-thoracic CT scan and 18 FDG PET scan showed no recurrence or residual tissue at the site of first resection or distally. A parathyroid scintigraphy identified abnormal uptake adjacent to the superior-medial pole of the left thyroid lobe, suggesting the presence of a parathyroid adenoma at this level. This single localisation was confirmed by PET methionine. A significant PTH gradient was also observed in the left superior cervical vein at selective venous sampling. The patient underwent cervical exploration with selective resection of a left superior parathyroid adenoma of 20x12x7 mm, without evidence of malignancy at pathological examination. This second surgery led to a sustained normalization of calcemia.
Discussion
We report the case of a patient with a double parathyroid pathology: a large right mediastinal parathyroid carcinoma followed by a benign left parathyroid adenoma which was diagnosed two years later. Parathyroid carcinoma is a rare cause of hyperparathyroidism with an incidence of 0.3 to 2.1%[1]. This large malignant tumour induced a severe parathyroid crisis, which nowadays accounts for less than 10% of the initial clinical manifestations, whereas renal and bone involvements are respectively found in 32–80% and 34–91% of cases[2,3]. The recommended treatment is surgical and should consist in a total *en-bloc* resection[3,4]. Chemotherapy and radiotherapy give disappointing results[3], while immunotherapy may prove beneficial but inconsistently[5]. The post-operative evolution was marked by a hungry bone syndrome, as it can occur classically after parathyroidectomy for severe and longstanding hypercalcemia[6]. The evolution was also complicated by the lack of long-term calcium normalisation which raised suspicion of a cancer relapse, but finally led to the diagnosis of the benign parathyroid adenoma.
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034

An unusual case of pubertas tarda: IGSF-1 deficiency syndrome
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Background aim of the work
IGSF-1 encodes a plasma membrane immunoglobulin superfamily glycoprotein that is abundant in the pituitary and testis. Loss-of-function causes an X-linked syndrome which is mainly characterized by congenital hypothyroidism and macroorchidism.[1,2] Because of its relatively recent discovery and its very rare incidence, the time to diagnosis is often long. We present a case of IGSF1 deficiency case where it took 6 years before diagnosis was made. With this report, we want to highlight the clinical and laboratory features of this syndrome.
Case presentation
A 16-year-old boy was seen at the Department of Endocrinology because of poor genital development and delayed growth since the age of 13. Besides a recently treated left varicocele, he had no significant medical history. At physical examination, standing height was 176.9 cm, body weight 62.6 kg, pubertal stage A1P2G2 and testicular volume 8 and 8 ml. His bone age was 12 years. At initial hormonal work-up LH was 2.5 U/l, FSH 2.6 U/l, PRL 85 mU/l (86-324), FT4 0.83 ng/dl (0.93–1.6) and testosterone 58.4 ng/dl (280–1110). A gonadotropin-releasing hormone stimulation test revealed a LH peak of 13.2 U/l and a FSH peak of 4 U/l. He was treated with 125 mg of Sustanon every 4 weeks during 6 months, inducing a catch-up growth in height and penile growth, and pubic hair development.
Two years later, his height was 191.4 cm, pubertal stage A2P4G3, testicular volume 15 and 15 ml and bone age 15 years. Basal FSH was 14.6 U/l (1.5–12.4), LH 4.9 U/l, and testosterone 358 ng/dl. No further measures were taken at that time.
Finally, at the age of 22 years, when his testis volume had increased up to 25 and 30 ml, basal hormonology confirmed central hypothyroidism (TSH 2.82 mU/l; FT4 0.89 ng/dl; FT3 0.19 ng/dl (0.0–0.44)), a persisting slightly elevated FSH (13.6 U/l), a low normal testosterone (263.3 ng/dl) and low DHEAS (157 µg/dl (211–492), but normal LH and SHBG levels. TSH increased up to 9.3 U/l 60 min after TRH and FSH up to 20.9 U/l after LHRH. Magnetic resonance imaging of the hypothalamic pituitary region was normal, except for a small lesion (5 mm). Treatment with levothyroxine was started.
The central hypothyroidism, hypoprolactinemia, poor adrenache and increasing FSH values in combination with delayed puberty and the post pubertal onset of macro-orchidism led to the suspicion of IGSF-1 deficiency. Saenger sequencing (Department of Genetics, Leiden) confirmed a loss-of-function mutation (c. 1030C>T; p.Arg344*) in the IGSF-1 gene.
Conclusions
Clinicians should be aware of the possibility of IGSF-1 deficiency syndrome in male patients with the combination of delayed puberty, central hypothyroidism and post pubertal macro-orchidism.[1,2]. Screening for carriership within family members is advised, since even in hemizygote females a higher incidence of central hypothyroidism, prolactin deficiency and delayed menarche is described.[2,3]
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035

CREST syndrome diagnosed because of faulty point-of-care glycaemia: a case report
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Background
Glycaemia point-of-care testing (POCT) is performed with fingerstick capillary whole-blood glucose measurement. These values normally correlate well with plasma glucose values. Hypoglycemia can be observed with POCT but should always be confirmed on plasma. True hypoglycemia must meet Whipple's triad: signs/symptoms of hypoglycemia; low plasma glucose; improvement after glucose administration. Artifactual hypoglycemia is defined as a discrepancy between POCT and plasma glucose measurements[1]. This can occur in cases of decreased capillary flow which leads to deceleration of glucose transit through tissues and consequently increased extraction by the tissues[1,2]
Case Presentation
A 86-year-old woman was admitted because she fell in her nursing home. Primary assessment POCT measured a glucose of 20 mg/dl. However, the patient expressed no clinical signs of hypoglycemia. Plasma glucose measurement was 91 mg/dl. She had no history of diabetes mellitus, nor of malignancy or auto-immune disease. HbA1c measured 42 mmol/mol. C-peptide was never elevated. POCT was compared multiple times with plasma glucose and showed regular discrepancy. POCT using blood from the ear lobe however correlated strongly with plasma glucose. Clinical examination revealed sclerodactyly and Raynaud's phenomenon. Raynaud Phenomenon and sclerodactyly is associated with artifactual hypoglycemia[1,3,4,5]. Further work-up for systemic disease revealed she had complaints of dysphagia. She featured facial telangiectasia. She had positive ANF-antibodies and anti-centromere antibodies. The patient was therefore clinically diagnosed with CREST syndrome, the limited cutaneous variant of systemic sclerosis. Due to the sclerodactyly, capillary blood flow is decreased, therefore the rate of tissue glucose withdrawal is increased[3,5].
Conclusions
POCT is useful to check glucose values. However, artifactual hypoglycemia can occur in settings of decreased capillary flow or increased glycolysis. Patients presenting with measured hypoglycemia but without symptoms of hypoglycemia

do not fulfill Whipple's triad and should raise suspicion for other etiologies. Connective tissue diseases such as systemic sclerosis are rare but can falsify capillary glucose. Serum glucose must be compared with POCT to objectify true hypoglycemia.

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036

Medullary thyroid carcinoma in two patients with neurofibromatosis type 1

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Introduction
Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous disorder characterised by the appearance of multiple, mostly benign, tumours throughout the skin and central nervous system. Furthermore, NF1 is associated with a number of (pre)malignant tumours including pheochromocytoma, glioma, invasive breast cancer and (pre)malignant peripheral nerve sheath tumours (1). Approximately 1:2500 to 1:3500 individuals are affected.
Medullary thyroid carcinomas (MTCs) are rare tumours, accounting for less than 2 percent of all thyroid cancers (incidence around 0.2/100 000 py (2)). Although the coexistence of NF1 and MTC has only rarely been described, a possible role for the NF1 gene mutation is suggested in the pathogenesis of MTC.
Clinical cases
(1) A 45-year old women attended the obesity clinic. Her clinical exam was remarkable for multiple café-au-laits spots and cutaneous neurofibroma's. Her family history included similar skin lesions in her father and two brothers, one brother had suffered from a brain tumour at age 9. NF1 had been diagnosed based on Ferner's criteria. On clinical examination a left sided thyroid nodule was noticed. Neck ultrasound showed a 2.5 cm hypoechoic hypervascular nodule in the left thyroid lobe and an ipsilateral suspicious lymph node in level 3. Fine needle aspiration and a high serum calcitonin concentration (518 pg/ml, normal value 0–15 pg/ml) were diagnostic of MTC. 24 hour urinary catecholamines and (nor) metanefrines were normal. A total thyroidectomy with central and left lateral lymph node dissection was performed. Pathological examination confirmed the diagnosis of MTC (T1N0). The postoperative calcitonin was undetectable.
(2) A 81-year old woman presented with weight loss, dysphagia and high CEA. Multiple facial cutaneous neurofibromas had been present since age 17, her father had had similar skin nodules but none of her 7 siblings had. Neck palpation revealed a 3 cm left sided thyroid nodule. Neck ultrasound showed a highly suspicious hypoechoic thyroid nodule with microcalcifications and irregular margins, a contralateral suspicious lymph node in level 6 and an ipsilateral pathologic lymph node in level 3. Serum calcitonin was high (1.721 pg/ml). 24 hour urinary catecholamines and (nor) metanefrines were normal. A total thyroidectomy with central and left lateral lymph node dissection was performed. Anatomopathology confirmed MTC (pT2N1). Postoperative calcitonin level was 29.7 pg/ml consistent with minimal residual disease.
Conclusion
NF1 can be considered as a tumour predisposition syndrome caused by constitutional mutations in the NF1 gene. This hereditary disorder is proven to be associated with a higher incidence of several malignancies (1). Up until now, MTC has not been proven to be one of them. Nevertheless the presence of NF1 in 2 patients of a consecutive series of 19 MTC in a single centre (2002–2018) is striking. NF1 is the commonest 'RASopathy', a group of syndromes caused by hyperactivation of the RAS/MAPK pathway (neurofibromin downregulates RAS, defective neurofibromin causes RAS activation) (3). Besides the genomic landscape of MTC has been deciphered and 20% of sporadic MTC harbour H or K-RAS mutations (whereas 50% of sporadic MTC harbour somatic RET mutations) (4). These molecular findings, the co-occurrence of NF1 and MTC in our two cases and (at least) 5 other cases in the literature warrant research into a possible association.

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037

The phenotypic diversity of the 22q11.2 deletion syndrome and hypoparathyrodism

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The 22q11.2 deletion syndrome is a clinical syndrome caused by a hemizygous deletion in the chromosome 22q11.2. Clinical findings include cardiac defects, characteristic facial features, thymic hypoplasia, cleft palate, hypoparathyroidism, learning difficulties and psychiatric disorders. The importance of chromosome 22 relies on small number of genes located in the long (Q) arm participating in the development of the body plan, including the pharyngeal arches during the embryonic development. The deletion of this genes can lead to a broad phenotypic heterogeneity resulting in a variety of abnormal clinical features, severity and time of onset, making the diagnosis and management a challenge. Examples of this deletion syndrome are the Velocardiofacial syndrome and the DiGeorge syndrome. We describe three patients, of which two adults and one child, with a proven 22q11 deletion who present different clinical characteristics but all having hypoparathyroidism in common. The first patient is a 64-year-old female who at 34 years of age suffered from a grand mal seizure attributed to a hypocalcemia of 4.8 mg/dl (normal range 8.5–10.2 mg/dl. Information regarding parathyroid hormone and phosphate are not available). The diagnosis of a primary hypoparathyroidism was made, for which treatment with calcitriol and calcium carbonate was started. Nine years later she was diagnosed with an auto immune negative subclinical hypothyroidism (TSH = 4.0 mU/l) at our out-patient clinic for which treatment with L-thyroxine was started. She has been a patient of our clinic since 1990. It was only in 2016 when a suspicion of a genetic cause for the combination of hypothyroidism and hypoparathyroidism was made. A 22q11.2 deletion syndrome was confirmed in 2018. Since 1989 she has not have any other seizures and no other organs affected by this syndrome have been reported. Our second patient is a 54-year-old male known to have renal abnormalities (bilateral urethra stenosis with hydronephrosis), severe mental retardation, deafness, repetitive otitis and upper airway infections during childhood, arterial hypertension, Graves hyperthyroidism treated by total thyroidectomy after a long treatment with thiamazol and a history of seizures attributed to hypocalcemia of as low as 6.7 mg/dl when the patient was 37 years old before the thyroidectomy was performed (phosphorus was 5.7 mg/dl, information regarding parathyroid hormone is not available). At this age the diagnosis of an autoimmune polyendocrine syndrome was presumed, given the association with hypocalcemia due to hypoparathyroidism and the presence of antiparietal cell antibodies. It was only in 2016 when a clinical suspicion of a genetic cause for his complex medical history was made, and the diagnosis of a 22q11.2 syndrome was made. Treatment with L-thyroxine, calcitriol and calcium carbonate are well tolerated, but patient needs constant surveillance for this treatment. Our third patient is a 12-year-old male born at 40 weeks of pregnancy. One month after birth he was hospitalized due to a viral gastroenteritis and bronchiolitis. He has a history of repetitive upper respiratory infections and retarded psychomotor development, there is no failure to thrive. At one year of age, he was again hospitalized because of convulsions, which were attributed to a hypocalcemia of 1.62 mmol/l (normal range 2.19–2.64 mmol/l) due to hypoparathyroidism (parathyroid hormone at presentation was 7.3 ng/l,

normal range between 15 and 65 ng/l). Phosphate was elevated (2.55 mmol/l, normal range between 1.07 and 1.74 mmol/l). The diagnosis of congenital hypoparathyroidism was made and genetic testing confirmed the clinical suspicion of a 22q11.2 deletion syndrome. Treatment with calcitriol and calcium carbonate was started. No other episodes of seizures followed under this treatment. Our aim is to emphasize the detection of development of hypocalcemia throughout the lifetime of patients with this syndrome, the importance of an early recognition and a multidisciplinary follow-up.

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038

Pheochromocytoma-induced Takotsubo syndrome: when you hear hoofbeats, it may be a zebra!

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Pheochromocytoma is a rare catecholamine-secreting tumor with variable clinical manifestations. A possible cardiac presentation is acute left ventricular wall motion abnormality in the heart also known as the Takotsubo syndrome. Takotsubo stress cardiomyopathy was first described in 1990 in Japan and current knowledge remains limited. We report a case of pheochromocytoma-induced Takotsubo syndrome. A 43-year-old woman acutely developed nausea, severe chest pain, and dyspnoea during a strenuous hiking-trip in the mountains. She arrived at our hospital in cardiac shock with need for invasive ventilation and hemodynamic monitoring. The ECG revealed an ectopic atrial rhythm, poor R-wave progression, and a prolonged corrected QT-interval. Chest X-ray showed pulmonary oedema. Troponin level was 2.42 µg/l (normally <0.005 ng/l) and NT-proBNP was 39.061 ng/l (normally <125 ng/l). Echocardiography documented severely impaired left ventricular function with basal and mid segmental akinesis and preserved contractility of the apex. Coronary angiography ruled out significant coronary disease. Ventriculography confirmed 'inverted' Takotsubo cardiomyopathy. Because of refractory high blood pressure, a diagnostic work-up was performed. 24-hour fractionated urinary metanephrine and normetanephrine levels were 7.483 and 8.895 µg/g creatinine respectively (normally <240 µg/g creatinine and <600 µg/g creatinine). Contrast-enhanced total body CT scan identified a left adrenal heterogenous mass of 59×56 mm. The diagnosis of pheochromocytoma was suggested. Adequate alpha-adrenergic blockade was ensured and laparoscopic adrenalectomy was performed. Pathological examination revealed nests of polygonal cells with eosinophilic cytoplasm. Immunohistochemical staining was strongly positive for chromogranin A and S100, confirming the diagnosis of pheochromocytoma. A rapid cardiac recovery was observed after tumor removal with complete recovery of ventricular wall motion and function. Pheochromocytoma-induced Takotsubo syndrome is very rare. Many stress factors have been identified as possible causes, and hypercatecholaminemia due to a secreting pheochromocytoma is one of them. This case presents a clear example of a physical trigger preceding the Takotsubo syndrome. Pheochromocytoma-induced Takotsubo syndrome may deteriorate more rapidly than other Takotsubo syndrome cases, with possible catastrophic presentations as in our case. We suggest screening for an underlying pheochromocytoma in Takotsubo syndrome, especially in younger patients, complicated or recurrent cases, in atypical (inverted/basal or global) Takotsubo subtypes and when other suggestive symptoms of pheochromocytoma are present.

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039

Severe hypocalcemia after a single denosumab injection and tumor-induced persistent hypophosphatemia in a patient with metastatic prostate cancer

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Case report

A 81-year-old male patient suffering from a Gleason 9 pT3aN0M0R1 prostatic adenocarcinoma was treated with radical prostatectomy and adjuvant radiotherapy in 2014. He presented in outpatient clinic for lumbar pain in October 2018. A 18F-NaF PET/CT showed diffuse metastatic bone involvement. Laboratory results showed hypophosphatemia (0.52 mmol/L, N: 0.75–1.39), normal renal function, normocalcemia (2.35 mmol/L, N: 2.20–2.55), normal 25-OH vitamin D (36 µg/L, N: 30–80), elevated total alkaline phosphatase (ALP) (1211 U/L, N: 56–119) and elevated prostate-specific antigen (PSA) (940 ng/ml, N<6.5 µg/L). Castration treatment with a GnRH antagonist was initiated. A single denosumab (anti-RANKL antibody) injection was administered on January 18 2019 in combination with 1200 mg of phosphorus-element supplementation. 32 days after denosumab injection, he presented with severe symptomatic (limb paresthesia and QT prolongation at 510 ms on electrocardiogram) grade 3 hypocalcemia at 1.59 mmol/L and grade 4 hypophosphatemia at 0.15 mmol/L, requiring hospitalization. The other blood tests showed: elevated serum parathyroid hormone (PTH) (125 ng/dl, N < 49), high serum levels of bone formation markers; osteocalcin at 46 µg/L (N: 14–46) and bone ALP at 91 µg/L (N: 5.5–22.9), low serum bone resorption marker; C-Telopeptide at 0.06 µg/L (N: 0.1–0.6), suppressed calciuria (<0.12 mmol/l), a paradoxical increase in phosphaturia (54 mmol/L) compared to serum hypophosphatemia, normal 25-OH vitamin D (50.4 µg/l), low 1,25-OH vitamin D (23.8 ng/l, N: 29–83.6) and increased serum levels of fibroblast growth factor 23 (FGF23) (393 pg/mL, N: 23–95). The patient required administration of intravenous (IV) calcium gluconate up to 8 g per day in addition to oral calcium citrate 6 g per day, IV and oral phosphorus and alphacalcidol at 2 µg per day for 14 days to resolve symptoms and normalize QT interval. He was discharged with persistent hypocalcemia (2.04 mmol/L) and hypophosphatemia (0.28 mmol/L). Serum calcium and PTH levels eventually normalized in June 2019 on ongoing oral supplementation, 6 months after denosumab injection, while hypophosphatemia is persistent to date. Metastatic bone disease showed progression at the last oncological evaluation in May 2019.

Discussion and physiopathological explanation

In our patient, suffering from high-burden metastatic bone disease, severe hypophosphatemia preexisted to denosumab injection and persists to date. It is probably caused by high serum FGF23 levels and low active 1,25 OH vitamin D indicated tumor-induced osteomalacia as a result of tumor FGF23 hypersecretion. The action of FGF23 on phosphocalcic metabolism is essentially due to its phosphaturic action with no direct effect on calcium metabolism. Severe hypocalcemia, despite increased serum PTH levels, suppressed calciuria and IV calcium administration at high doses, was attributed to denosumab itself which is a potent inhibitor of osteoclast-mediated bone resorption leading to highly increased influx of calcium into bone. Denosumab-induced hypocalcemia is more frequently described in case of vitamin D deficiency and impaired renal function that were not present in our patient. However, male sex, osteoblastic metastases, high serum PSA levels and high bone turnover, as in the case of our patient, have been recently shown to increase the risk for denosumab-related hypocalcemia.

Conclusion

This case illustrates that patients with castration-resistant metastatic prostate cancer should be carefully monitored in clinical practice for potentially severe calcium-phosphate homeostasis disorders: We observed in this patient a persistent hypophosphatemia induced by FGF23 hypersecretion and a denosumab-induced hypocalcemia. This case illustrates that in the context of high-burden bone disease, one single injection of denosumab may induce severe hypocalcemia even in the absence of vitamin D deficiency or renal function impairment. Whether increased secretion of FGF23 is a risk factor for Denosumab-induced hypocalcemia is not addressed in the literature but it is well known that FGF23 inhibits renal production of 1,25-dihydroxyvitamin D and at least in patients with normocalcemia conditions an inhibitory effect on PTH secretion.

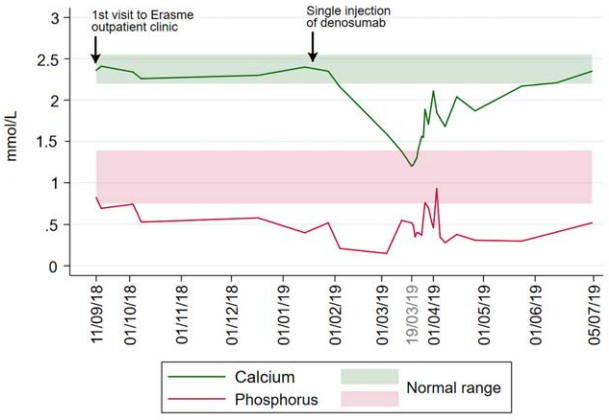

Figure 1 Calcemia and phosphatemia during the time.

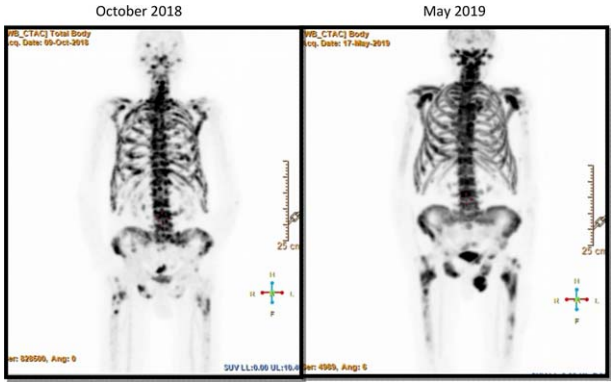

Figure 2 Images of the A18F-NaF PET/CT.

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040

Prepubertal gynecomastia: what to suspect first?

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Introduction
Most cases of prepubertal gynecomastia are classified as idiopathic. However, an exogenous or endogenous hyperestrogenism (from estrogen producing testis or adrenal tumors) has always to be excluded. Other rare underlying endocrine causes are congenital adrenal hyperplasia, aromatase excess, hyperthyroidism and hyperprolactinemia[1,2].
We report a transient hyperprolactinemia, beside other ignored clinical and hormonal signs of estrogen impregnation, in a prepuberal boy investigated for gynecomastia as an alarming sign of hyperestrogenism, related to indirect exposure to a nonformulary estrogen cream in the mother.
Case report
A 9 year and 10 month old boy was referred for non-prolactinoma related hyperprolactinemia. He presented with a recent history of bilateral breast enlargement and slight pubic hair development. He had no previous medical or surgical history. His father had no gynecomastia during childhood or adolescence. Neither a familial history of precocious puberty or Peutz-Jeghers syndrome was present. He had no neurological or ophthalmological complaints. Gynecomastia and areolar pigmentation was noted for two months, but without body odor or axillary hair development. He had been taken commercial Perilla oil tablets, for 6 months, because of diminished concentration and memory, but these supplements had been stopped one month before the breast development. He did not take any other food supplements or herbal products. He was not using cosmetic ointments or any medications since the start of gynecomastia. He had a normal diet.
Biochemical evaluation showed a normal BUN, creatinine and transaminases, but slightly elevated alkaline phosphatases (450 IU/L). Hormonal analysis showed an elevated prolactin (29 µg/l (4–15.2), a slightly elevated TSH (5.85 ng/l (0.6–4.8), normal FT4, normal cortisol and undetectable gonadotrophins and estradiol. A MRI of the pituitary was normal. Bone age was 11.5 years.
At referral, body height was 144 cm, weight 33 kg and blood pressure 125/65 mmHg. Tanner stage was A1P2G1. Testes were 3 ml without palpable nodules. Bilateral breast development was scored as Tanner 3 stage with 4 cm of glandular tissue and dark brown areolar pigmentation. No galactorrhea was present at breast manipulation. No thyromegaly, hepatosplenomegaly and cutaneous lesions or aberrant skin pigmentation were present.
Repeated basal hormonology showed a normal PRL (11 µg/l) TSH, DHEAS, androstenedione, 17-OH progesterone, estradiol, estrone, testosterone and β-hCG, but a very high SHBG (500 nmol/l) and suppressed FSH (0.1 IU/l) and unmeasurable LH (<0.1 IU/l). Ultrasound of the testes and adrenal were normal. During the GnRH stimulation test, no LH and FSH response were observed.
On obtaining further history, his mother confirmed that she was using for several months before the breast development a nonformulary estrogen cream, obtained at an anti-aging clinic. Handwashing after cream application was not always performed and she and son were using the same towels. The mother was asked to stop the estrogen applications. To further control the effects of suspected estrogen contamination and limit further excessive bone maturation, letrozole was administered for 4 months with a rapid regression of the gynecomastia. Bone age did not progress after 6 months and pubic hair disappeared, while the intense areolar pigmentation remained.
Discussion
The areolar hyperpigmentation made us to suspect rather hyperestrogenism as an underlying cause for the gynecomastia, in addition of the typical hormonal profile, showing completely suppressed gonadotrophins, both at baseline and after GnRH stimulation, and the very elevated SHBG. Prolactin elevation has been observed after high estrogen exposure in men, as in transgenders[3]. Also the contrasting finding of pubic hair and normal adrenal androgens is an additional argument for exposure to estrogens in our patient, since pubic hair growth can be seen by treating patients with gonadal dysfunction with estrogens[4].
The use of estrogen cream was initially not disclosed by the mother, but was afterwards confirmed by her and the prescribing physician. We cannot exclude some priming role of the use of perilla seeds, known to have a high content of phytosterols, especially B sitosterol[5].
Beside indirect exposure to nonformulary estrogen cream used by mothers as hormone replacement, estrogen contaminated poultry as well hair cream has been reported other sources of exogenous estrogens leading to prepubertal gynecomastia[6,7]. These potential estrogen sources were not revealed by the boy and his mother. On the other hand, repeated topical application of product containing laverder and tea tree oils, having both estrogenic and antiandrogenic activities, are another reason for breast development in males, but were not used by our patient.
Bone age advancement by cutaneous estrogen application is especially apparent in prepubertal children, who in addition are also more likely to develop gynecomastia than adolescents because of unopposed effects of testosterone. Non-classical adrenal hyperplasia and aromatase excess can also present with gynecomastia, early pubic hair development and advanced bone maturation[8,9]. The normal adrenal androgen as well as the normal estradiol and estrone concentrations do not support the diagnosis of these diseases.
In conclusion, in the evaluation of prepubertal gynecomastia, not only the use of cosmetics, herbal medicines or topical medications, including estrogens should not only be questioned in the child, but also in the parents and other close caregivers.
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