GROWTH AND PUBERTY IN THE DIAGNOSIS OF MEN1-RELATED MANIFESTATIONS DURING CHILDHOOD

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List of abbreviations

MEN1 syndrome	Multiple Endocrine Neoplasia type 1 syndrome
pHPT	Primary Hyperparathyroidism
PA	Pituitary Adenoma
NET	Neuroendocrine Tumor
PanNET	Pancreatic Neuroendocrine Tumor
NF	Non-functioning
ACTH	Adrenocorticotropic hormone
MRI	Magnetic Resonance Imaging
CT	Computed Tomography
EUS	Endoscopic Ultrasound
M1-5	Mammae 1-5 (Tanner stages)
DMSG	Dutch MEN1 Study Group
N	Number
SDS	Standard Deviation Score
IQR	Interquartile Range
SD	Standard Deviation
KM analysis	Kaplan-Meier analysis
95% CI	95% Confidence interval
UMCU	University Medical Center Utrecht
WKZ	Wilhelmina Children Hospital

Abstract

Introduction

MEN1 syndrome exhibits early manifestations including primary hyperparathyroidism (pHPT), pituitary adenomas (PA) and neuroendocrine gastrointestinal tumors (PanNET). While these manifestations are often asymptomatic before age 19, symptomatic cases may require intervention. Current guidelines recommend annual clinical and laboratory assessments with additional imaging for PA and PanNET.

Purpose

To determine age-dependent penetrance of the primary MEN1 manifestations and investigate the efficacy of relying solely on symptoms, growth assessment and pubertal development to detect clinically relevant manifestations.

Methods

We conducted a retrospective study on a cohort from the Dutch MEN1Study Group (DMSG), comprising of MEN1 patients from UMC/WKZ. The study involved periodic screening during childhood and adolescence, collecting additional data on growth and pubertal development, and symptoms. Age-dependent penetrance of MEN1 manifestations was estimated using Kaplan-Meier analysis. Linear growth, onset of puberty, manifestations and intervention were visually represented through plots.

Results

Among 44 patients, 52% developed pHPT before age 19, 30% had PA and 21% had PanNET. Patients with manifestations exhibited varied linear growth. Out of 22 patients identified for growth/pubertal development analysis, two, with MEN1-related manifestations, displayed decelerated growth during puberty, necessitating intervention for functioning PA.

Conclusion

The predominant MEN1 manifestation was pHPT, followed by PA and PanNET. Symptomatology was minimally indicative for pHPT and not for PanNET. Patients with functioning PA exhibited delayed puberty and growth deceleration. Monitoring growth and biochemical parameters exclusively can indicate functioning PA in this cohort. Further research in a larger cohort is necessary to establish the contributory value for patients.

Introduction

Multiple Endocrine Neoplasia Type 1 (MEN1) is a rare autosomal dominant syndrome primarily characterized by the presence of parathyroid, pituitary, and gastropancreatic neuroendocrine tumors.[1–5] MEN1, is caused by germline heterozygous loss-of-function mutations in the tumor suppressor gene *MEN1*.[3,5,6] Since the implementation of presymptomatic genetic testing in 1997, coupled with the introduction of periodic screening guidelines in 2001, more data and knowledge are accessible for MEN1 in children and adolescents.[1,2,5,7]

Current MEN1 diagnostic guidelines recommend initiating screening for primary hyperparathyroidism from the age of eight, relying on annual biochemical analyses.[5] Screening for pituitary adenomas is recommended in a similar manner with the addition of annual magnetic resonance imaging (MRI), starting from the age of 5.[5] Based on the current guidelines, the screening for pancreatic neuroendocrine tumors is advised with the implementation of annual biochemical tests from the age of 5 and abdominal MRI, computed tomography (CT) or endoscopic ultrasound (EUS) every three years, depending on the type of tumor.[5]

Early manifestation of MEN1 in childhood primarily include primary hyperparathyroidism (pHPT), typically presenting asymptomatic even in the presence of (mild) hypercalcemia.[3] In the case of symptomatic hypercalcemia, the most common symptoms include malaise, constipation, polyuria and/or polydipsia.[3] Clinical symptoms of pituitary tumors, which are mostly non-functioning, are depended on the secreted hormone (e.g. prolactinomas, growth-hormone secreting, ACTH secreting adenomas) and the size of tumor, potentially leading to headache, galactorrhea, delayed puberty and visual field abnormalities.[3,8] Similarly, neuroendocrine gastrointestinal tumors cause symptoms depending on their type. However, these tumors are most commonly non-functioning and thus asymptomatic. Most often insulinomas are presented in patients under the age of 20, while gastrinomas and other types are not well-described in pediatric patients.[3]

A timely diagnosis of MEN1 is crucial for prompt surveillance, with the potential need for subsequent interventions. However, recurrent medical surveillance post-diagnosis, involving yearly biochemical analyses and imaging, may contribute to an accumulation of psychological burden to any patient, particularly the young.[9] With the accumulated screening starting from young age, based on the current guidelines, the question arises: Are all biochemical analyses and imaging necessary for identification of clinically relevant manifestations? Thus, we studied if exclusive symptom monitoring, along with pubertal and growth assessment, is sufficient for detecting clinically relevant manifestations in children and adolescents with MEN1.

The aim of this study is twofold. First, we aimed to determine the age-dependent penetrance of the three main MEN1 manifestations, namely the pituitary adenomas (PA's), primary hyperparathyroidism (pHPT) and the pancreatic neuroendocrine tumors (PanNET's) among University Medical Centre Utrecht (UMCU)/Wilhelmina's Children Hospital (WKZ) patients prospectively screened in childhood/adolescence. Secondly, we explored whether we might

rely on symptoms and assessment of growth and pubertal development to detect clinically relevant manifestations.

Methods

Study population

For the current study, patients with genetically conformed MEN1 from the UMCU/WKZ part of the Dutch MEN1 Study Group (DMSG) database were identified.[10] We included patients who were periodically screened during childhood and adolescence, as well as those who came to attention before the age of 19 because of manifestation. Childhood and adolescence were defined as age below 19. For this study, follow-up was until either reaching the age of 19 or October 1st, 2023, whichever came first. We included patients born in 1985 or later, because longitudinal data collection of the DMSG database started in 1990, to ensure availability of childhood data. For the study of growth and pubertal development, we only included patients with available height measurements during puberty as well as parental height. Patients included in the DMSG database have provided informed consent for the use of the data for MEN1-related research.

Data collection

The Dutch MEN1 Study Group (DMSG) database has near complete capture of all MEN1 patients in the Netherlands.[10] Data from identified patients (laboratory results, pathology reports and radiological imaging) was systematically collected for every quarter of every available year of follow-up from 1990-2014. From 2014 onwards the database was migrated to Castor EDC, with clinical data systematically collected for each identified patient based on occurrence date rather than on a quarterly basis. The DMSG methodology has been extensively described elsewhere.[11] The study protocol was approved by the Medical Ethical Committees of all UMCs in the Netherlands.[10]

For this specific study additional clinical data was collected on the included patient regarding linear growth (length Standard Deviation Score [SDS] and target height SDS based on measurements of parental height), pubertal development (Tanner stages and menarche) and symptoms. The following symptoms were scored per manifestation: headache, visual field abnormalities, galactorrhea and Cushingoid features for PA's, gastrointestinal symptoms, symptomatic kidney stones, polyuria/polydipsia, fatigue, sleep- or mood disorder for pHPT and gastrointestinal symptoms for PanNET's. [3] For data analysis, data were extracted from the DMSG Castor online database and analyzed alongside the additional dataset collected.

Data definitions and outcome measures

MEN1 diagnosis can be made based on genetic testing, clinical or familial criteria. A clinical diagnosis is indicated by the presence of two or more MEN1-related tumors, while familial criteria are fulfilled if a patient exhibits one MEN1-related manifestation and has a first-degree relative with MEN1.[3]

For the purpose of this study, onset of pHPT was defined as the first of two consecutively elevated calcium measurements (either ionized or albumin-corrected total), with elevated or inadequately normal PTH.[10] A PA was considered present if twice consecutively seen on imaging, with onset defined as the first positive imaging.[10] Microadenomas were defined as adenomas smaller than 10 mm, while macroadenomas from 10 mm or greater. A PanNET was deemed to be present if observed consecutively on imaging on two separate occasions, with onset defined as the first instance of positive imaging.[10]

Tumors observed in patients with MEN1 were categorized as either functioning or non-functioning (NF) depending on symptoms and laboratory results. NF PA were defined as tumors not associated with clinical evidence of hormonal hypersecretion. Prolactinomas, the predominant functioning PA, was defined by two consecutive measurements of elevated serum prolactin levels. Adenomas producing growth-hormone (acromegaly) or adrenocorticotropic hormone (ACTH) associated with Cushing's disease were diagnosed based on current guideline recommendations.[5] The most frequently encountered functioning PanNET in MEN1, insulinoma, was diagnosed by characteristic symptoms combined with the finding of hypoglycemia with inappropriately elevated insulin.[5] Gastrinomas were identified by elevated fasting serum gastrin.[5]

The onset of puberty in females was defined by the realization of Tanner stage 2 in mammary development (M2).[12] In males, puberty was defined by the achievement of testicular volume exceeding three milliliters.[13]

The data for monitoring patients in childhood and adolescence was collected until the age of 19. However, in instances where surgical or pharmaceutical interventions took place shortly after the age of 19, these intervention-related data were incorporated into the analysis and depicted in plots. Therefore, the upper limit for age monitoring in such cases was defined at 21 years.

Statistical analysis

For descriptive analysis, means, standard deviations (SD) and, in the case of non-normally distributed data, medians and interquartile range (IQR) were used for continuous data. For categorical data frequencies were used. For the assessment of age-related penetrance of manifestations, we used Kaplan-Meier (KM) analysis. All analyses were performed using IBM SPSS Statistics for Macintosh, Version 24.0 (Armonk, NY: IBM Corp) and visualized with GraphPad Prism (version 10.1.2).

To visualize linear growth in the entire cohort a spaghetti plot was created for boys and girls separately. Additionally, plots were generated for each individual patient, displaying linear growth and including marks for onset of puberty, manifestations, and intervention. For the visualization of the plots regarding parameters of growth and pubertal development GraphPad Prism (version 10.1.2) was used.

Results

Characteristics of the studied cohort

A total of 211 patients with MEN1 syndrome were identified in the UMCU/WKZ. After exclusion of n = 167 either because the date of birth was before January 1985, diagnosis and follow-up was initiated after the age of 19 or other reasons, a total of 44 patients could be included for analysis of manifestations during childhood (Figure 1). As data on pubertal growth and/or parental height (and thus target height) were partly unavailable, only 22 out of 44 patients, could be included to analyze the association between clinically relevant MEN1 manifestations in pubertal development and growth symptomatology.

The demographic characteristics of the studied cohort, as described in Table 1, exhibit a balanced sex distribution with 23 males (52.3%) and 21 females (47.7%). Out of the diagnosed MEN1 patients, 43 were identified through genetic testing, and one case with familial criteria. The mean age at MEN1 diagnosis was 10.5 (SD +/- 4.5). Children visited a pediatric endocrinologist for the first time at the mean age of 12 years (SD +/- 4.5). As of October 1st, 2023, the median age at the end of the follow-up period was 18.9 (IQR 15.0 – 18.9). 61% had reached the age of 19, 39% was still 18 years or younger as of October 1st, 2023.

Among the cohort of 44 patients, 13 (30%) individuals developed pituitary adenomas, 23 (52%) primary hyperparathyroidism and 9 (21%) were diagnosed with pancreatic neuroendocrine tumors during childhood and adolescence. Overall, 61% of the children was diagnosed with one or more manifestations.

Pituitary adenoma

Out of 44 patients, 38 (86%) had a pituitary MRI scan during childhood at a mean age of 15 years (SD +/- 2.4) for the first MRI, while the youngest age a patient had a first scan was almost 11 years. The mean age at diagnosis of PA in the 13 diagnosed patients was 16.2 years (SD +/- 1.7). Most PA's were non-functioning (n = 8, 61.5%), followed by prolactinomas (n = 4, 3%) and one case of Cushing's disease (7.7%). Out of all PA's, 85% were microadenomas. Results of the KM analysis (figure 2A) show that the predicted probability of being diagnosed with a pituitary adenoma at the age of 19 is 42%. Regarding symptoms we had no data on 3/13 patients. Three patients were symptomatic at diagnosis: one exhibited headache, another displayed Cushingoid features, and the third experienced both headaches and visual field abnormalities. The majority of diagnosed PA patients were asymptomatic at diagnosis (n = 7/13, 53.9%). Of those patients, subsequently two patients developed headaches by the age of 19 (29%). Among those without PA, three patients had headaches and one (n = 1, 3.2%) exhibited symptoms of headaches and galactorrhea, while having negative imaging and not being diagnosed before the age of 19. The diagnosis of PA for this particular patient eventually was made at age of 23 years. Within the PA cohort, two patients underwent pharmaceutical intervention with cabergoline for the treatment of microprolactinoma, while one patient received treatment for galactorrhea, accompanied with hyperprolactinemia, despite the absence of an evident prolactinoma on imaging. Two patients underwent surgery before the age of 19, one diagnosed with a macroprolactinoma and the other with a micro ACTH-producing tumor.

Primary Hyperparathyroidism

Serum calcium was measured in almost all patients (n = 43/44). One child lacked calcium measurement, due to young age (aged 8 years at last follow-up).[5] Mean age at first calcium measurement was 11.9 years (SD +/- 4.3), while the youngest child started from the age of five years. Over half (n = 23, 52%) of the patients developed primary hyperparathyroidism (pHPT) during childhood and adolescence at a mean age of 14.9 years (SD +/- 2.5), ranging from 10.8 to 18.5 years. Results of the KM analysis (figure 2B) show that the predicted probability of being diagnosed with a pHPT at the age of 19 is 68%. Regarding symptoms, no data was available on 6/23 patients (26%). Among patients diagnosed with pHPT, seven manifested symptoms at the time of diagnosis: two patients had polyuria/polydipsia, four gastrointestinal symptoms, one fatigue and one both fatigue and gastrointestinal symptoms. However, most patients were asymptomatic at diagnosis (n = 10/23, 44%). Among the patients asymptomatic at diagnosis, two patients subsequently became symptomatic with gastrointestinal symptoms, one experienced fatigue and another one exhibited polyuria/polydipsia. Among the patients without pHPT during childhood and adolescence, three (n = 3/21, 14.3%) also complained of fatigue and six (n = 6/21, 28.6%) had gastrointestinal symptoms. Ten out of 23 (43%) children and adolescents diagnosed with pHPT were operated in adolescence. Following initial conventional neck exploration, three children required reoperation due to persistent hyperparathyroidism (hypercalcemia persisting < six months post-surgery).[14] Additionally, two children underwent reoperation after initially undergoing minimal invasive parathyroidectomy; one due to persistent hypercalcemia and the other due to recurrent hypercalcemia occurring more than six months post-surgery.[14] The mean age of patients undergoing surgery was 15.9 (SD +/- 1.9; range 12.3 – 18.7).

Neuroendocrine tumors

Similarly to pituitary adenoma (PA) evaluations, 86% of the cohort underwent screening for NET's with abdominal MRI scans (n = 38/44). The first MRI abdomen scan was obtained at a mean age of 13.7 (SD +/- 2.5), ranging from 7.6 to 18.3 years. Pancreatic neuroendocrine tumors (PanNET's) were identified in nine children (n = 9, 21%), all classified as non-functioning. The mean age at PanNET diagnosis was 15.4 (SD +/- 1.9), with the youngest age of 12.1 years. Results of the KM analysis (figure 2C) show that the predicted probability of being diagnosed with a PanNET at the age of 19 is 27%. At diagnosis, 56% were asymptomatic (n = 5). No data were available for four patients (n = 4, 44%). Out of the nine patients diagnosed with PanNET, one necessitated surgical intervention. Despite the initial diagnosis occurring in childhood, the surgical procedure was conducted shortly after reaching 19 years of age.

Growth & pubertal development

Out of the 22 patients for whom data on linear growth and pubertal development was available, 18 patients showed normal development. Two female patients (Figure 4A.6 and 4A.7) exhibited marked deceleration in longitudinal growth (n = 2/22, 9.1%), one other female patient (Figure 4A.4) showed small stature (n = 1/22, 4.5%) and one male patient (Figure 4B.6) demonstrated tall stature and growth exceeding the target height range (n = 1/22, 4.5%).

Figures 3A and 3B display the growth patterns related to target height and whether manifestations are present or absent during childhood and adolescence (with manifestations: blue line, without manifestations: black line). Figures 4A.1-11 and 4B.1-11 demonstrate individual plots for each of the 22 patients, categorized in females (females: n = 11/22, 50%) and males (males: n = 11/22, 50%), respectively.

Among the 22 patients studied for growth and pubertal development, six patients developed PA (n = 6/22, 27.3%), ten exhibited pHPT (n = 10, 45.5%), and five had PanNET (n = 5, 22.7%) during childhood and adolescence. Late onset of puberty was observed in three cases (Figure 4A.6, 4A.11 and 4B.11).

We now describe the two cases of growth deceleration in more detail.

The first case concerns a girl (Figure 4A.6) with genetically confirmed MEN1 syndrome, whose onset of puberty was at the age of 13.5 (M2). At the age of 14,5 years, she was diagnosed with a macro-prolactinoma. A second MRI showed size increase of the prolactinoma and because of delayed menarche, cabergoline was initiated at 17 years of age, resulting in menarche. At the age of 20 the macroprolactinoma was surgically removed via transsphenoidal resection.

The second case (Figure 4A.7) was a girl referred to the endocrine pediatric clinic for investigation of short stature at the age of 13. The MEN1 diagnosis was based on diagnosed pHPT and a parent with MEN1 (familial criteria). Due to a symptomatic presentation with pubertal stagnation and other Cushingoid features, investigation in the biochemical parameters found an elevated 24-hour urine cortisol. Imaging showed a micro pituitary adenoma, and the diagnosis of Cushing's disease was later also confirmed by sinus petrosus venous sampling. Around 14 years of age, she got diagnosed with pHPT and several months later she got a surgery for pHPT. The ACTH-producing pituitary adenoma was operated twice, due to failure of decreasing levels of cortisol around the age of 15. Data about puberty are not known, only that she reached M5 at almost age 17.

Discussion

In the present study, we retrospectively examined a cohort of 44 pediatric MEN1 patients from the DMSG database and found that overall, 61% presented at least one of the three most prevalent manifestations. More specifically, pHPT was developed in 52% of the cases, PA's in 30% and PanNET's in 21%. Interestingly, the higher prevalence of pHPT in our Dutch pediatric cohort is in line with reports of pHPT being the earliest MEN1 manifestation detected by biochemical examination of patients,[9] as well as what has previously been observed in pediatric and adolescent cohorts from the United Kingdom,[15] Germany,[16] Italy,[17,18] Australia,[19] as well as in grouped cohorts from France and Belgium,[7] as well as Austria, the United Kingdom, and the United States.[4] The same trend was observed within the subgroup of 22 patients included in our analysis of linear growth and pubertal development with pHPT in 46%, PA in 27%, and PanNET developed in 23% of the cases, indicating that despite its small size, this is a representative group of patients, appropriate for the intended analyses. Importantly, this seems to be the global trend, with PAs on the second place of prevalence, based on the recent review paper by Brandi et al., further validating our approach.

We found that mean ages of manifestation occurrence were 14.9 years (SD +/- 2.5) for pHPT, 16.2 years (SD +/- 1.7) for PA, and 15.4 (SD +/- 1.9) for PanNET. This is in agreement with the findings of Goudet et al., who reported a higher frequency of MEN1-induced lesion occurrence between the ages of 10 and 21 years of age.[7] However, our findings are contradictory to what was reported by Manoharan et al., who only rarely found severe manifestations at an age below 16 years old in a German cohort of 166 patients, arguing for routine screening of patients after this age.[16]

Remarkably, numerous manifestations were identified in this pediatric cohort, often asymptomatic and not requiring intervention. Nevertheless, timely detection of MEN1-associated manifestations remains important, as intervention proved necessary in almost half (43%) of pHPT cases, in almost one fourth (23%) of PA cases, and in one patient exhibiting PA symptoms, hyperprolactinemia, and negative imaging before age 19. Symptomatology had limited efficacy in identifying manifestations of pHPT and was not suggestive for PanNET.

In this regard, we found that the children with manifestations did present a greater variety in length SDS in comparison to the children without manifestations, indicating that the monitoring of growth might be a first indicator for such manifestations. It is noteworthy that all patients with decreased longitudinal growth and short stature did also present MEN1 manifestations, while the single patient with increased stature had no known MEN1 manifestations and symptoms. This further validates our hypothesis, suggesting that monitoring growth deviation could be exploited as a sign for further investigations of MEN1 manifestations. As the size of the cohort presented in this study was rather small, direct conclusions should not be drawn at this stage and additional analysis of the possible correlation is required.

Interestingly, growth deviation was observed only in clinically relevant functioning PAs, although not in all cases presenting functional PAs. In our cohort, several patients developed puberty and subsequently growth in the normal range of age and length SDS while also being diagnosed with functioning micro pituitary adenomas, namely micro-prolactinomas. These functioning micro-PA's seem not to contribute to the deviation of growth, contrary to the other functioning PA's, as we identified in the two cases of MENA048 and MENA049. This further indicates that growth deviation monitoring might not be sufficient for the prediction of micro prolactinomas, while being a good marker for other functional PAs.

Similar to micro prolactinomas, growth deviation is insufficient in signaling the presence of pHPT or PanNET. These two manifestations, nonetheless, remain crucial during childhood and adolescence in our cohort, as 10 patients with pHPT had a surgical intervention during this period, and one patient with PanNET was surgically treated just after the age of 19. In this respect, we should also stress the fact that our cohort lacks MEN1 patients presenting insulinomas or gastrinomas, thus no conclusion can be drawn on the possible earlier suspicion of functional NETs through growth monitoring or symptomatology.

In this study, our analysis presents some undeniable strengths: (i) to the best of our knowledge, we are the first to illustrate unique growth development data of 22 children with MEN1 syndrome, (ii) we took care to prospectively screen a well-defined group in a detailed, transparent manner that depicts their life-long (until the age of 19) clinical monitoring and (iii) all patient data was extracted from the same source, which was further derived from the same clinical center. Nonetheless, our study had also some limitations: (i) symptomatology and puberty (Tanner stages) was, in most cases, inadequately noted due to the retrospective nature of this study and (ii) the incomplete data could also lead to potential bias among physicians, especially if symptomatology was more comprehensively reported in patients with manifestations.

This unique set of data, although small in the context of this study, sets the foundation for other international studies in which the value of clinical follow-up of symptomatology, growth and puberty development parameters for detection of MEN1 related manifestations will be studied. Our preliminary results here make us optimistic that the detection of functioning PAs through exclusively monitoring growth and pubertal will further be validated during the wider screen, hopefully aiding in diminishing the burden of screening for the patients, while maximizing the chances of catching certain MEN1 manifestations early, further contributing to the management of the disease.

Conclusion

Overall, we have identified pHPT as the most prevalent and earlier-developed MEN1 manifestation in our Dutch pediatric cohort at the UMCU/WKZ and we have associated delayed puberty and growth deceleration with the existence of MEN1 related functioning PA. Early diagnosis is crucial, particularly for pHPT and functioning PA, as substantial interventions are frequently present. Symptomatology proves to be a limited indicator for pHPT and is entirely non-indicative for PanNET. Conversely, the monitoring of growth and pubertal development plays a contributory role in detecting functioning PA in this cohort. Consequently, it can be inferred that, exclusively for functioning PA, the monitoring of growth and biochemical parameters is vital in autonomously identifying clinically relevant cases. This latter observation, if verified in a larger cohort, might prove to be essential for limiting the burden of recurrent scans and hospital visits.

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Figures & Table

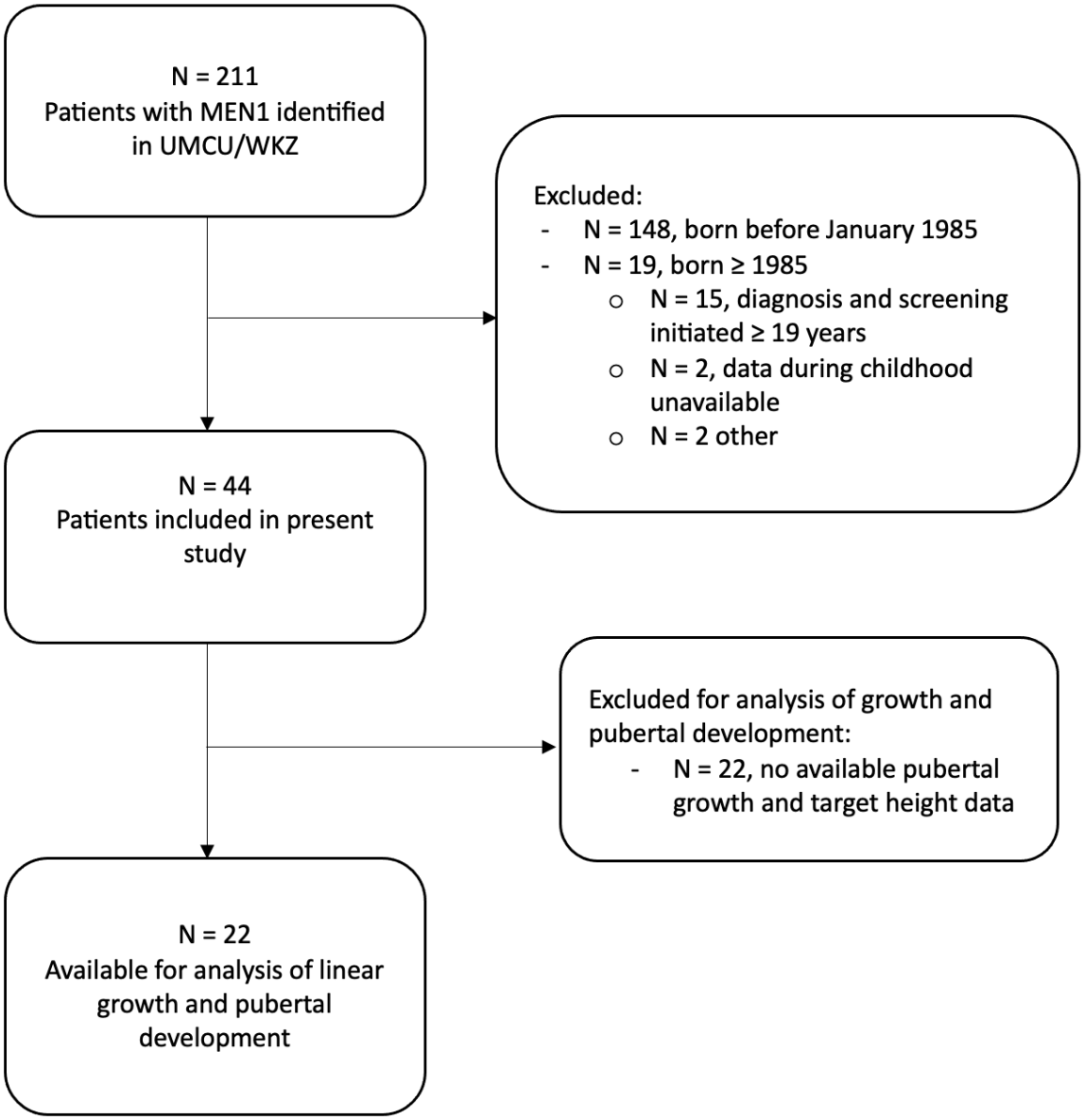
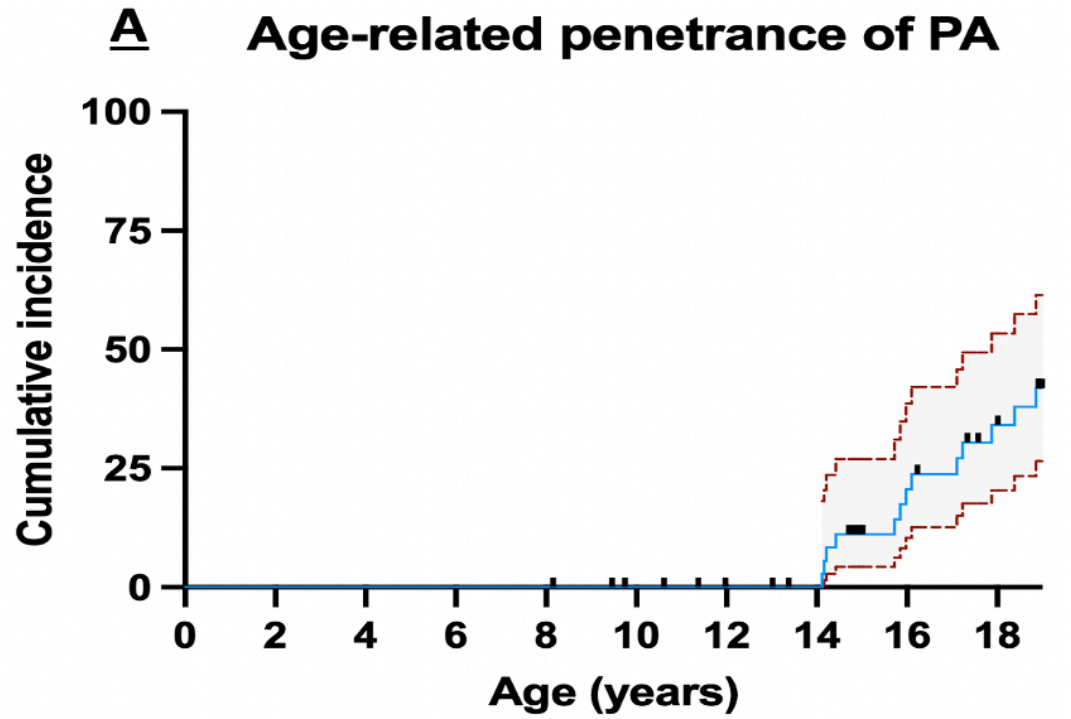


Figure 1. Flowchart of included patients. N = number.

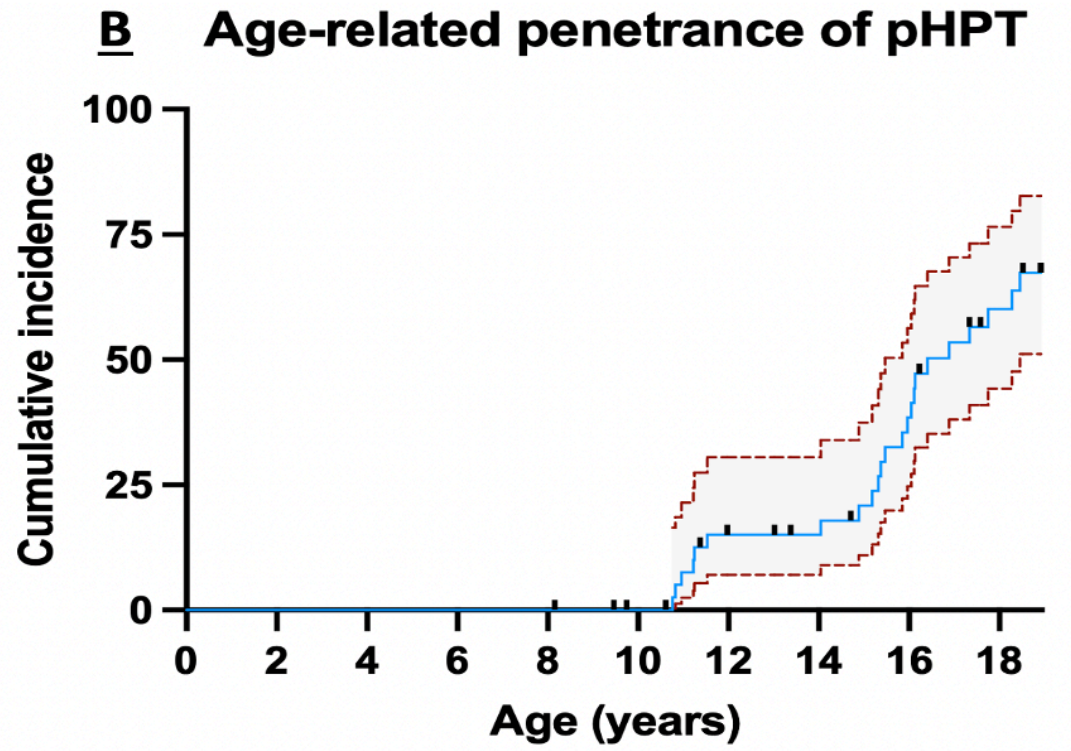
	All children
Sex (n = 44)	
Male, n (%)	23 (52.3)
Female, n (%)	21 (47.7)
Age at the end of follow-up, median (IQR; min - max)	18.9 (15.0 - 18.9; 8.15 - 18.9)
MEN1 diagnosis	
Age at MEN1 diagnosis, mean (SD; min - max)	10.5 (+/- 4.5; 1.7 - 18.3)
Method of MEN1 diagnosis	
Presymptomatic genetic testing, n (%)	43 (97.8)
Clinical, n (%)	0
Familial, n(%)	1 (2.2)
Age first visit pediatric endocrinologist, mean (SD; min - max)	12.0 (+/- 4.5; 5.0 - 18.3)
Manifestations	
Pituitary adenoma	
MRI pituitary performed, n (%)	38 (86.4)
Age first MRI, mean (SD; min - max)	15.1 (+/- 2.4; 10.8 - 18.8)
Diagnosis pituitary adenoma, n (%)	**13 (29.5)**
Age at diagnosis, mean (SD; min - max)	16.2 (+/- 1.7; 14.1 - 18.9)
Subtype	
Prolactinoma, n (%)	4/13 (30.8)
Non-functioning, n (%)	8/13 (61.5)
Cushing's Disease, n (%)	1/13 (7.7)
GH producing, n (%)	0
Micro-adenoma, n (%)	11/13 (84.6)
Macro-adenoma, n (%)	2/13 (15.4)
Symptomatology	
Symptomatic at diagnosis	
Yes, n (%)	3/13 (23.1)
Headache, n (%)	2/13 (15.4)
Visual field abnormalities, n (%)	1/13 (7.7)
Galactorrhea, n (%)	0
Cushingoid features, n (%)	1/13 (7.7)
No, n (%)	7/13 (53.8)
If no, symptoms before age 19	
Headache, n (%)	2/7 (28.6)
Visual field abnormalities, n (%)	0
Galactorrhea, n (%)	0
Cushingoid features, n (%)	0
No data, n (%)	3/13 (23.1)

Primary Hyperparathyroidism	
Serum Calcium measured < 19 years old, n (%)	43 (97.7)
Age first serum Calcium measurment, mean (SD; min - max)	11.9 (+/- 4.3; 5.0 - 18.6)
Diagnosis primary Hyperparathyroidism, n (%)	**23 (52.3)**
Age at diagnosis, mean (SD; min - max)	14.9 (+/- 2.5; 10.8 - 18.5)
Symptomatology	
Symptomatic at diagnosis	
Yes, n (%)	7/23 (30.4)
Gastro-intestinal, n (%)	4/23 (17.4)
Symptomatic kidney stones, n (%)	0
Polyuria/polydipsia, n (%)	2/23 (8.7)
Fatigue, sleep or mood disorder, n (%)	2/23 (8.7)
No data, n (%)	6/23 (26.1)
No, n (%)	10/23 (43.5)
If no, symptoms before age 19	
Gastro-intestinal, n (%)	2/10 (20)
Symptomatic kidney stones, n (%)	0
Polyuria/polydipsia, n (%)	1/10 (10)
Fatigue, sleep or mood disorder, n (%)	1/10 (10)
No data, n (%)	6/23 (26.1)
Neuroendocrine tumor	
MRI abdomen performed, n (%)	38 (86.4)
Age first MRI, mean (SD; min - max)	13.7 (+/- 2.5; 7.6 - 18.3)
Diagnosis neuro-endocrine tumor, n (%)	**9 (20.5)**
Age at diagnosis, mean (SD; min - max)	15.4 (+/- 1.9; 12.1 - 18.8)
Non-functioning, n (%)	9 (100)
Asyptomatic at diagnosis	
Yes, n (%)	5/9 (55.5)
No data, n (%)	4/9 (44.4)
Insulinoma, n (%)	0
Gastrinoma, n (%)	0
Growth	
Growth deceleration, n (%)	2 (9.1)
Short stature, n (%)	1 (4.5)
Tall stature, n (%)	1 (4.5)
Pubertal development	
Tanner stage ages	
Mammae (M) 2, mean (SD; min - max)	10.9 (+/- 2; 8.9 - 13.3)*
Testes volume > 3mL, mean (SD; min - max)	13.9 (+/- 2.1; 10.3 - 17.7)**
Age at menarche, mean (SD; min - max)	13.1 (+/- 1.7; 10 - 17.2)***
*based on 6 out of 15 females	
**based on 13 out of 16 males	
*** based on 12 out of 21 females	

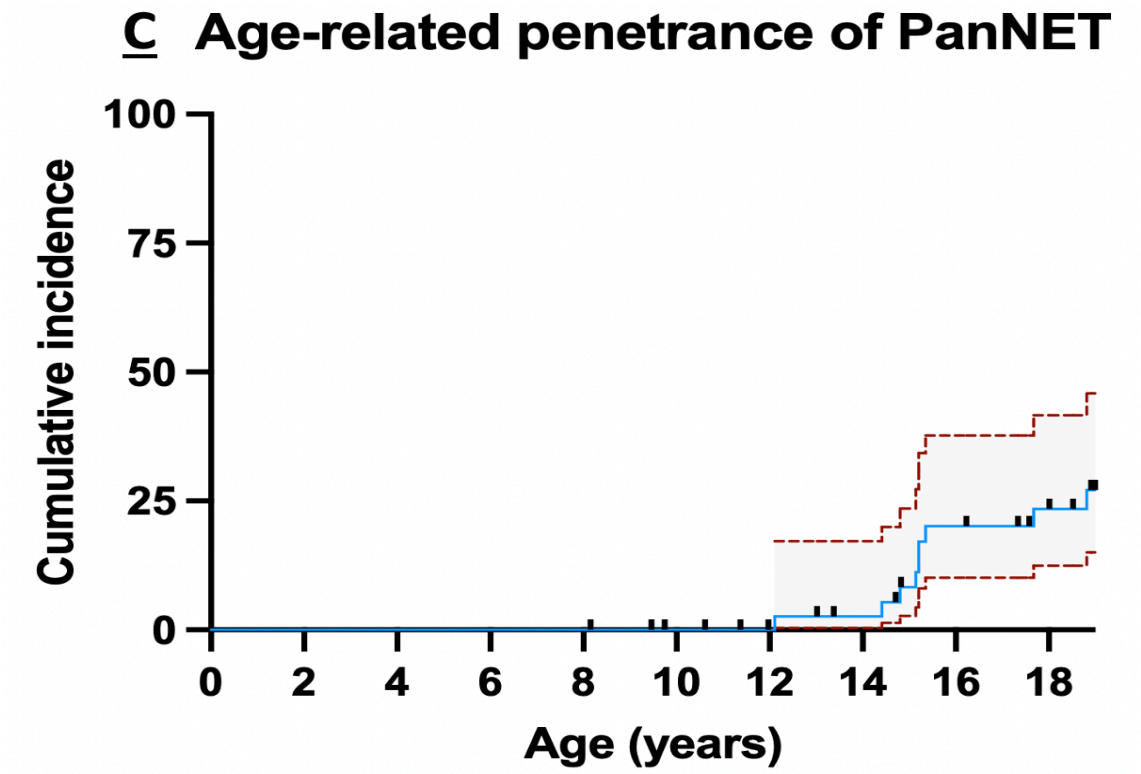
Table 1. Characteristics of cohort. n = number, SD = standard deviation.



No. at risk	44	44	44	44	44	41	39	36	25	18	15
Age (years)	0	2	4	6	8	10	12	14	16	18	19



No. at risk	44	44	44	44	44	41	33	30	21	11	8
Age (years)	0	2	4	6	8	10	12	14	16	18	19



No. at risk	44	44	44	44	44	41	38	35	27	23	20
Age (years)	0	2	4	6	8	10	12	14	16	18	19

Figure 2. Age-related penetrance of PA (A), pHPT (B) and PanNET (C). Blue line shows KM curve, red lines are 95% CI. Markers on blue line are censored cases.

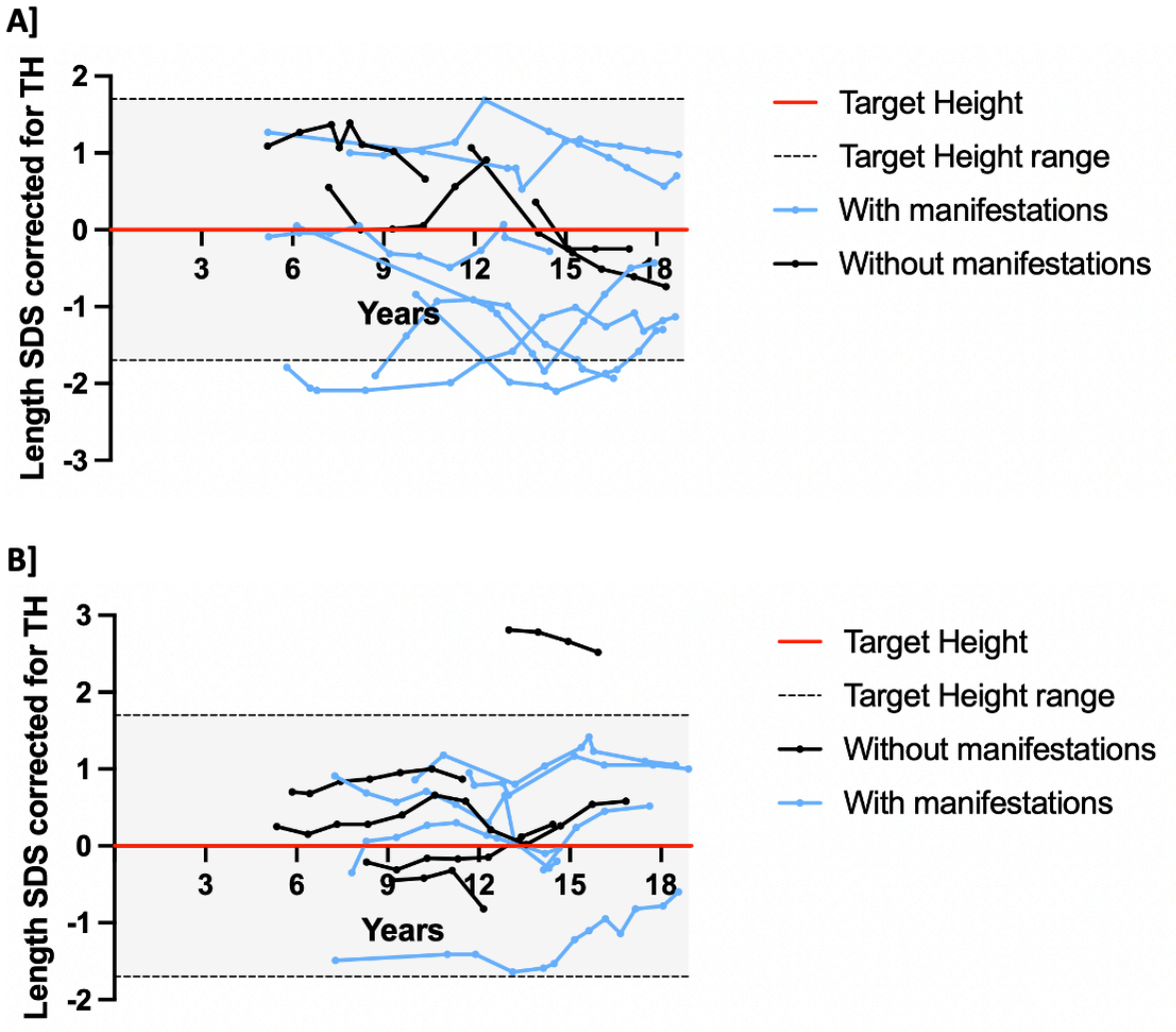
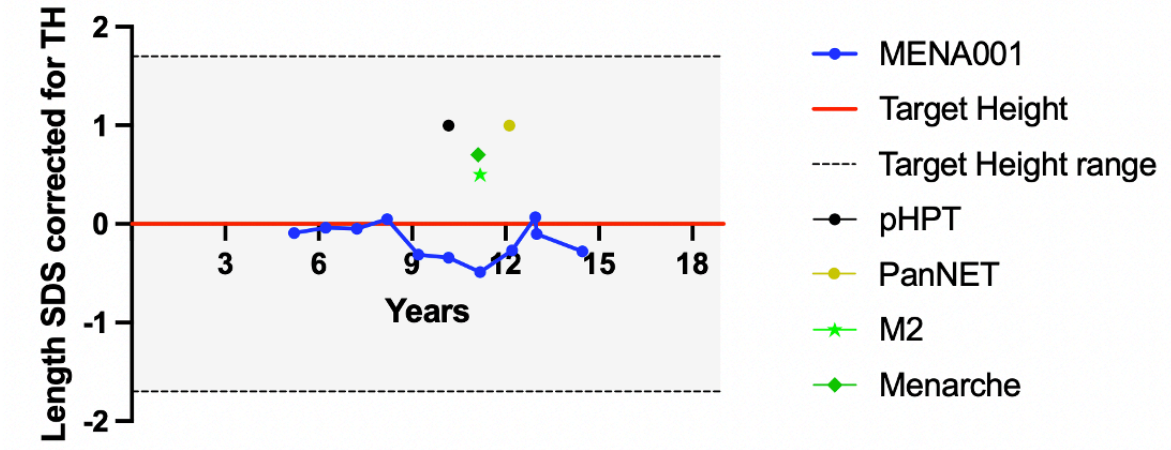


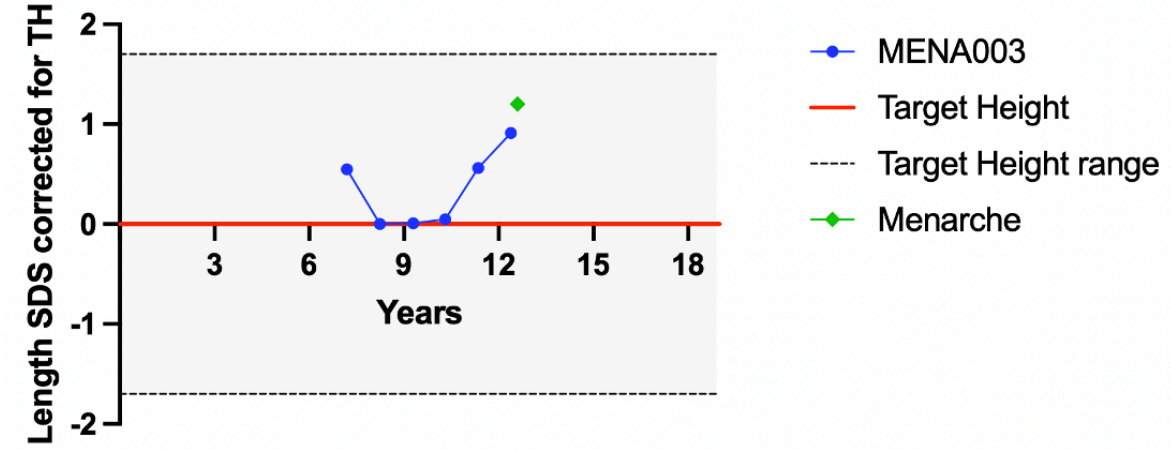
Figure 3. A] Females, B] Males. Spaghetti plots of length SDS corrected for target height related to age (years). Blue: with manifestations, black: without manifestations, red: target height.

A

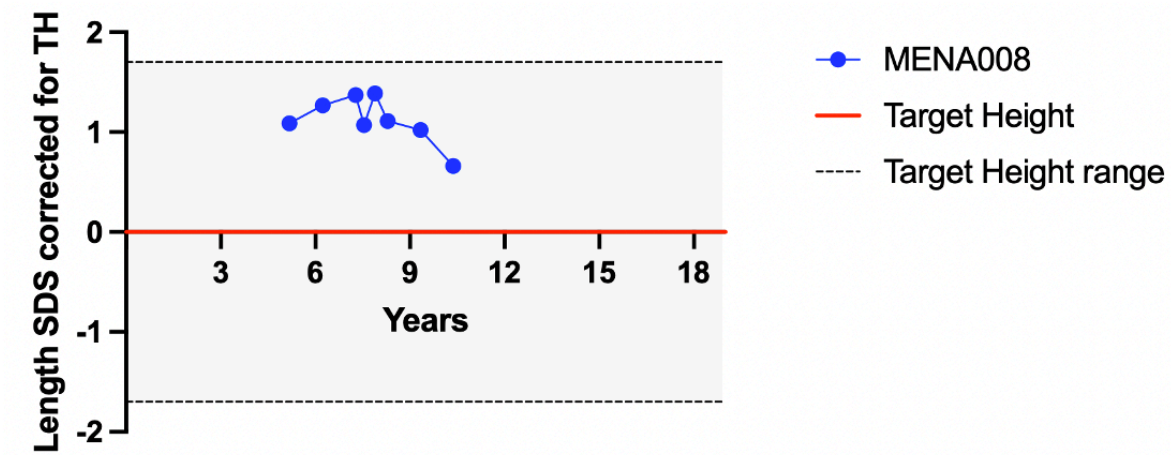
1]


Length SDS corrected for TH
2
1
0
-1
-2
3
6
9
12
15
18
Years
MENA001
Target Height
Target Height range
pHPT
PanNET
M2
Menarche

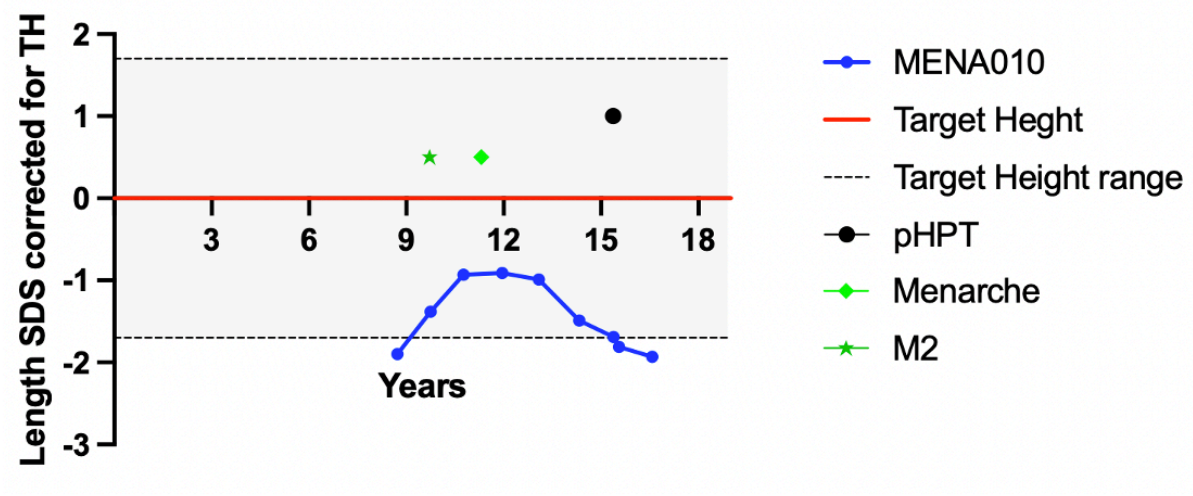
2]


Length SDS corrected for TH
2
1
0
-1
-2
3
6
9
12
15
18
Years
MENA003
Target Height
Target Height range
Menarche

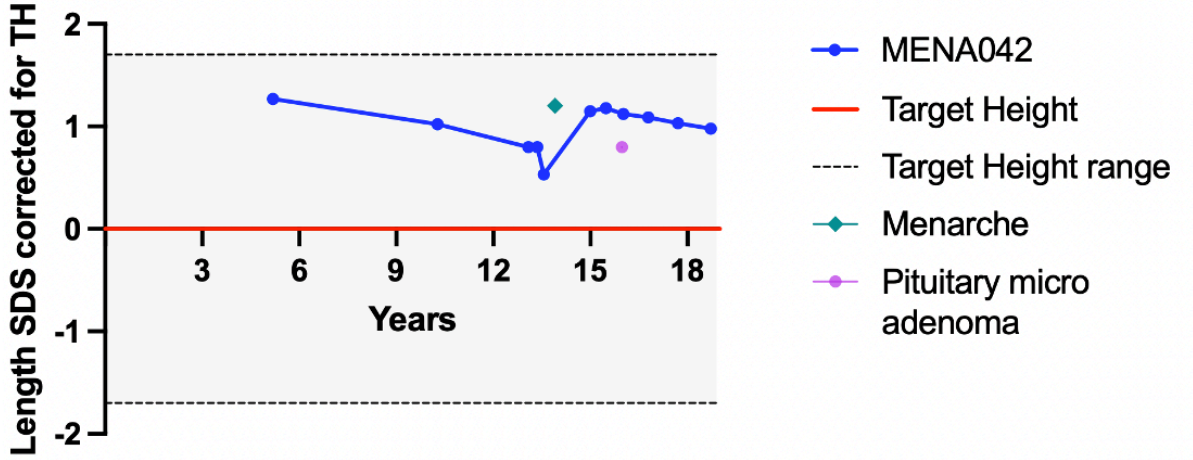
3]


Length SDS corrected for TH
2
1
0
-1
-2
3
6
9
12
15
18
Years
MENA008
Target Height
Target Height range

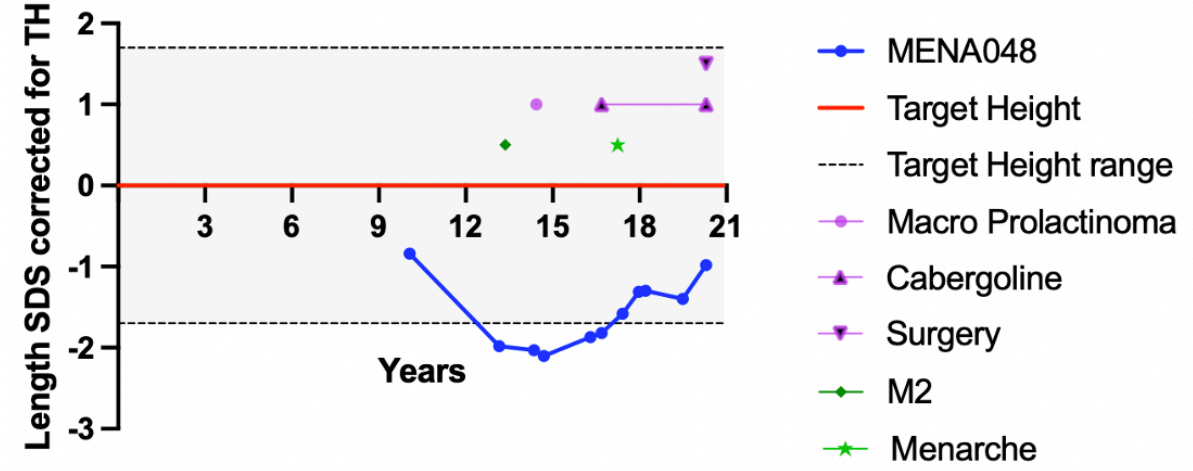
4]


Length SDS corrected for TH
2
1
0
-1
-2
-3
3
6
9
12
15
18
Years
MENA010
Target Heght
Target Height range
pHPT
Menarche
M2

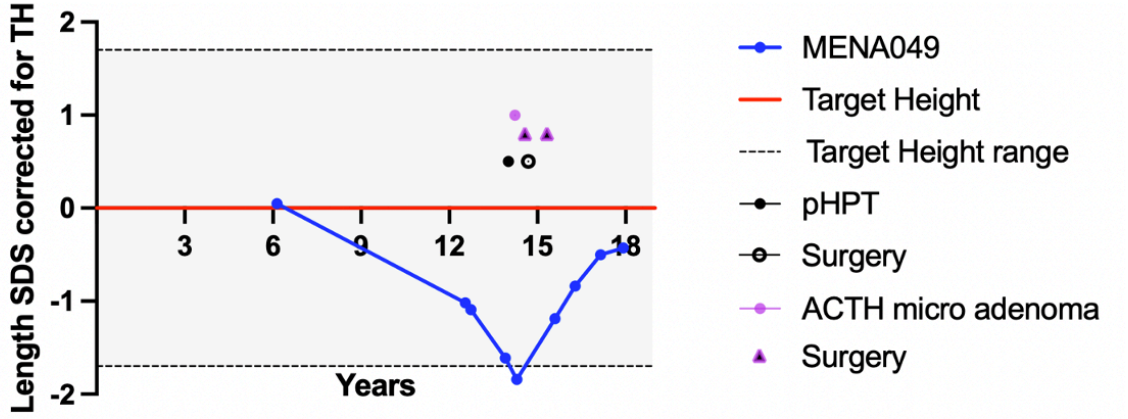
5]


Length SDS corrected for TH
2
1
0
-1
-2
3
6
9
12
15
18
Years
MENA042
Target Height
Target Height range
Menarche
Pituitary micro adenoma

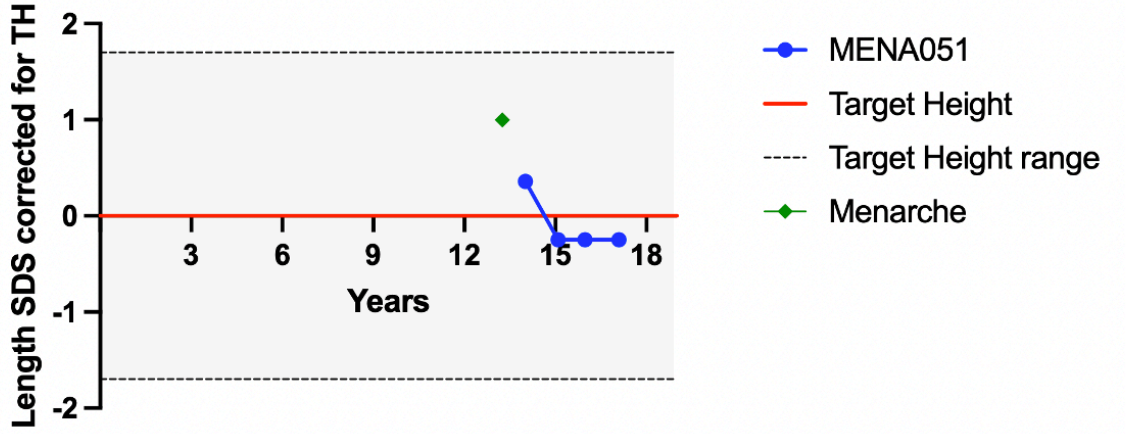
6]


Length SDS corrected for TH
2
1
0
-1
-2
-3
3
6
9
12
15
18
21
Years
MENA048
Target Height
Target Height range
Macro Prolactinoma
Cabergoline
Surgery
M2
Menarche

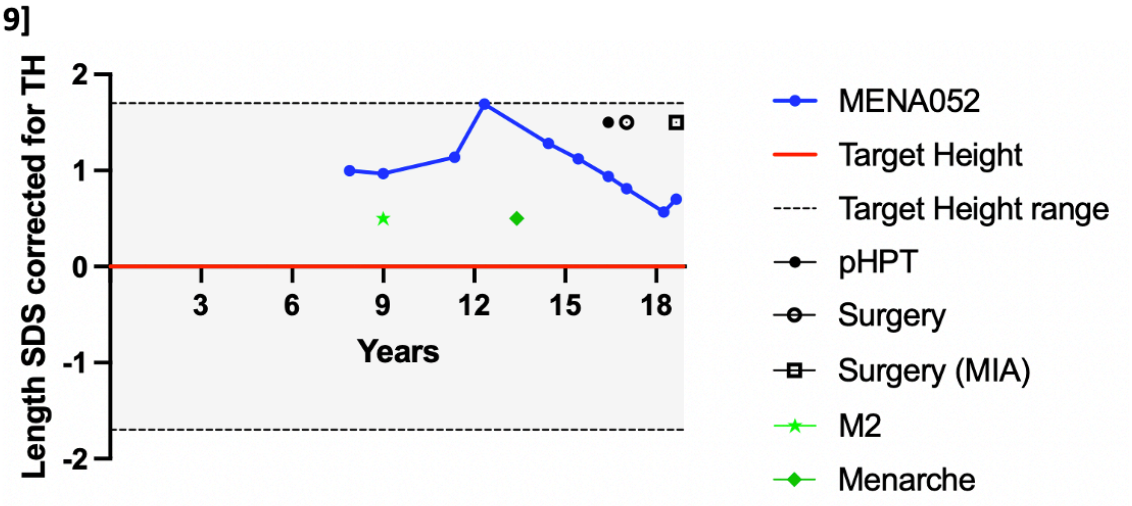
7]


Length SDS corrected for TH
2
1
0
-1
-2
3
6
9
12
15
18
Years
MENA049
Target Height
Target Height range
pHPT
Surgery
ACTH micro adenoma
Surgery

8]


Length SDS corrected for TH
2
1
0
-1
-2
3
6
9
12
15
18
Years
MENA051
Target Height
Target Height range
Menarche

9]


Length SDS corrected for TH
2
1
0
-1
-2
3
6
9
12
15
18
Years
MENA052
Target Height
Target Height range
pHPT
Surgery
Surgery (MIA)
M2
Menarche

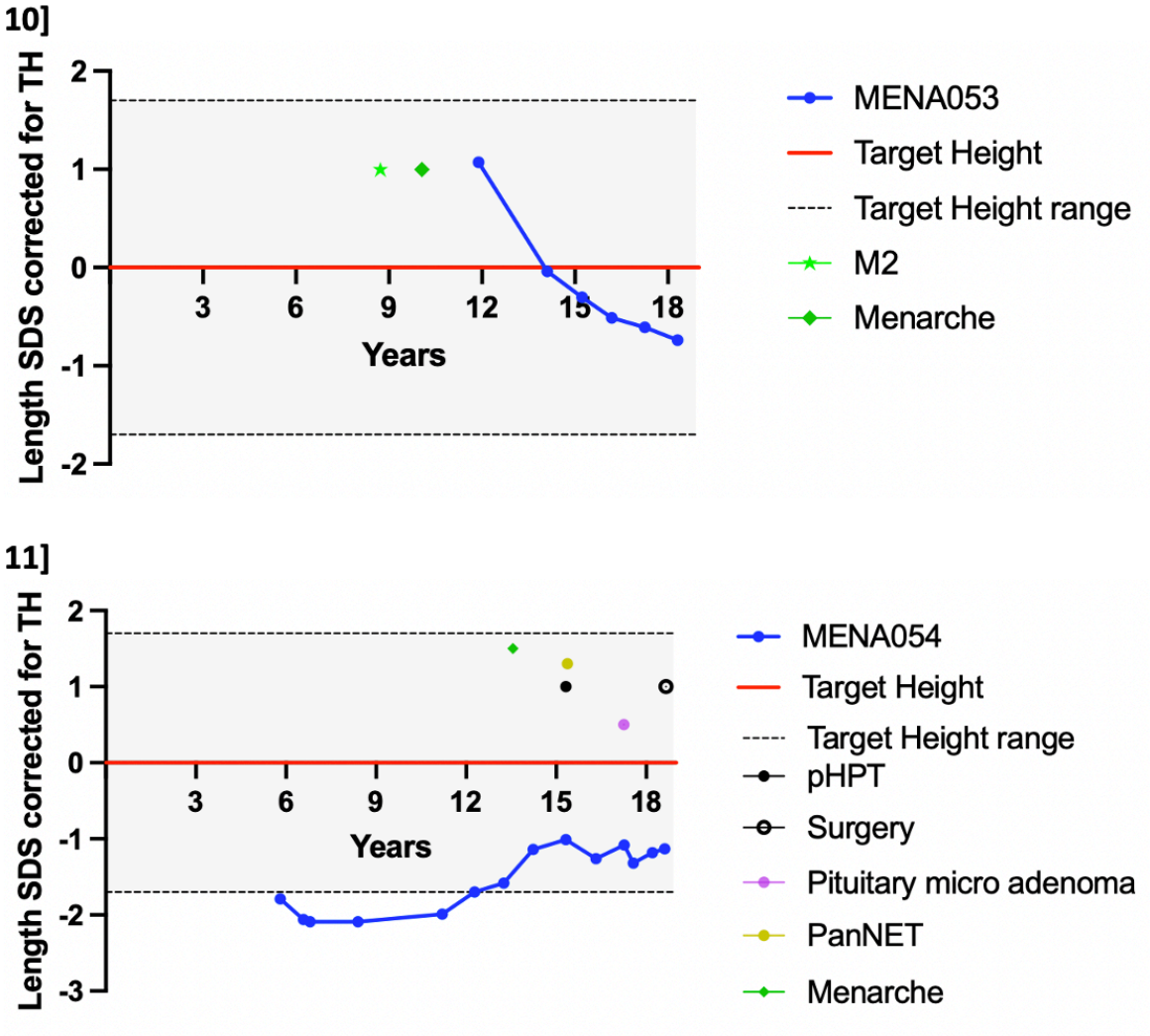
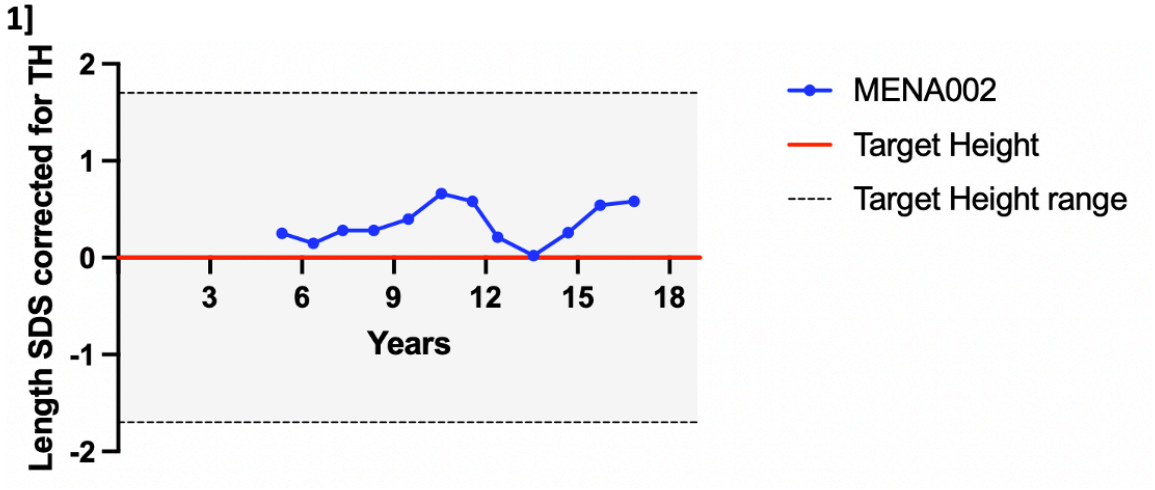


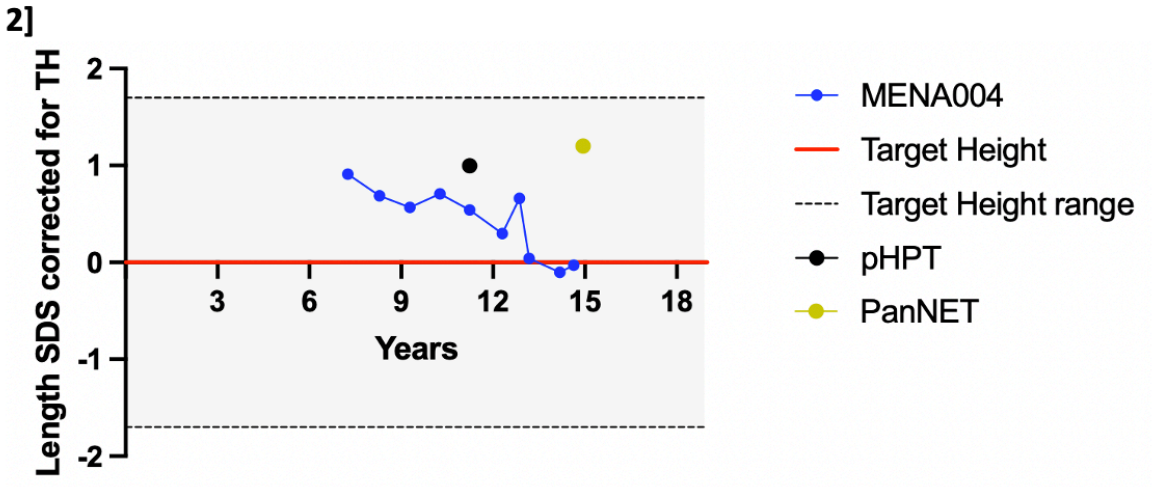
Figure 4. **A. 1] - 11]** Plots of each female patient with known growth/pubertal data, manifestations and intervention. Blue line = length SDS corrected for TH of patient, red line = target height; pHPT = primary hyperparathyroidism, PanNET = pancreatic neuroendocrine tumor, M2 = Mammae 2 (Tanner stages), MIA = minimal invasive adenomectomy.

B

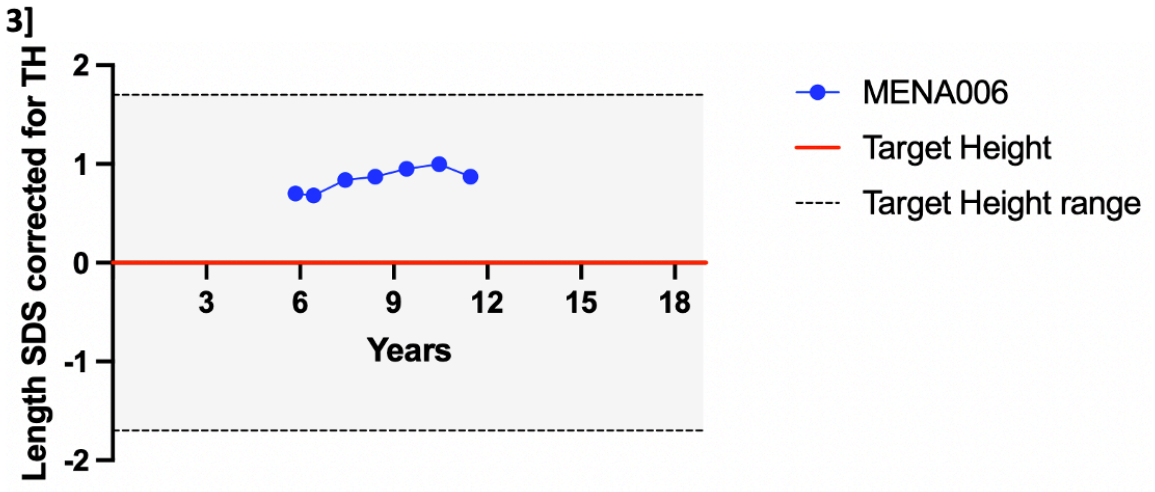
1]


Length SDS corrected for TH
2
1
0
-1
-2
3
6
9
12
15
18
Years
MENA002
Target Height
Target Height range

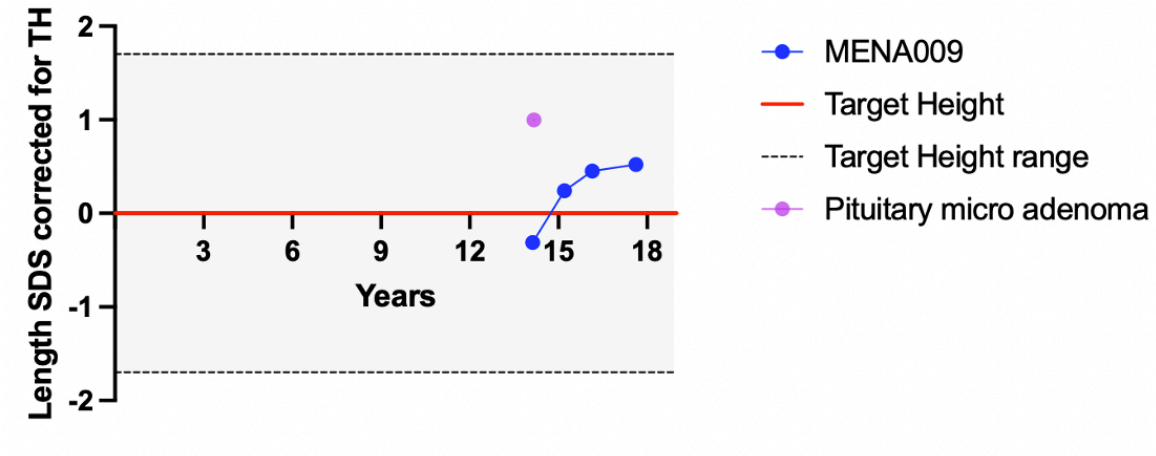
2]


Length SDS corrected for TH
2
1
0
-1
-2
3
6
9
12
15
18
Years
MENA004
Target Height
Target Height range
pHPT
PanNET

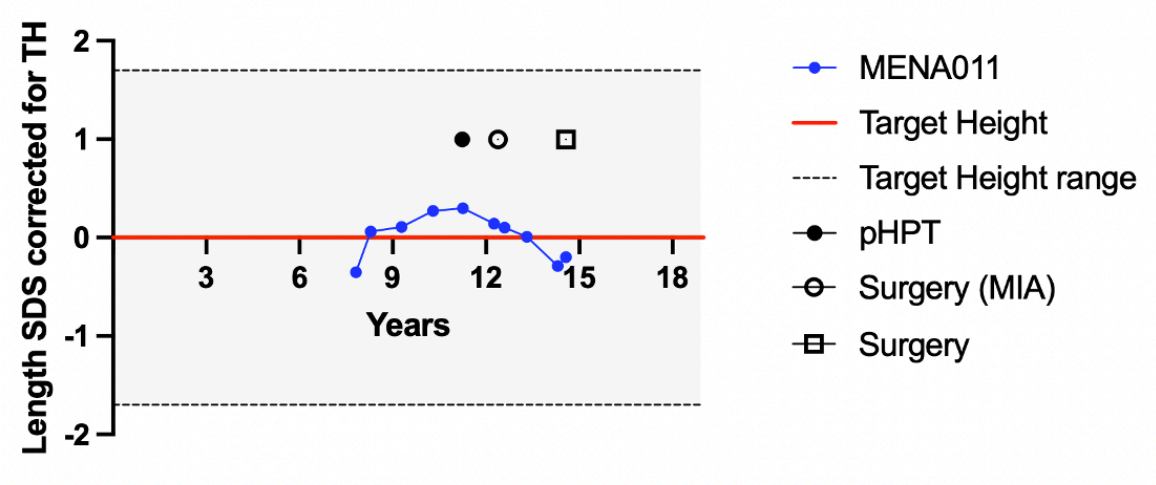
3]


Length SDS corrected for TH
2
1
0
-1
-2
3
6
9
12
15
18
Years
MENA006
Target Height
Target Height range

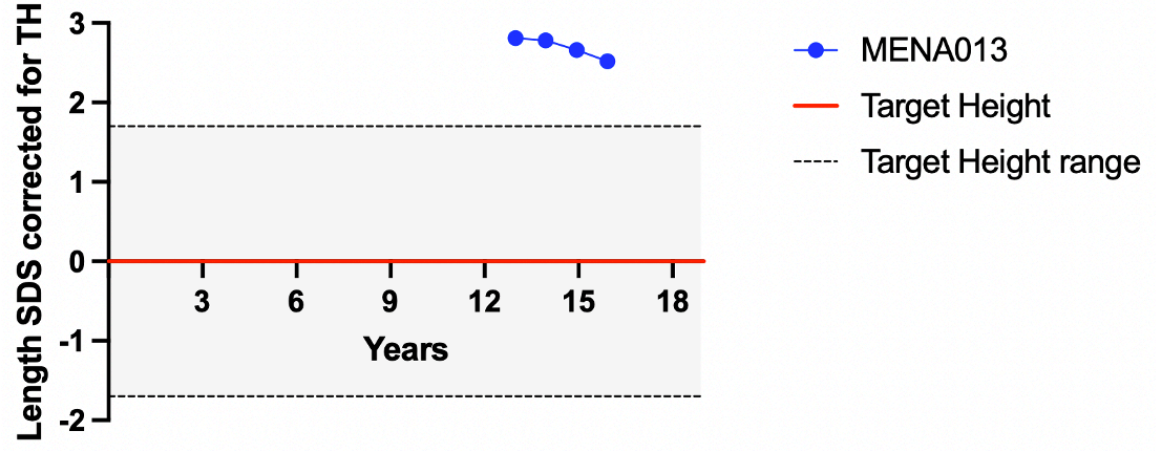
4]


Length SDS corrected for TH
2
1
0
-1
-2
3
6
9
12
15
18
Years
MENA009
Target Height
Target Height range
Pituitary micro adenoma

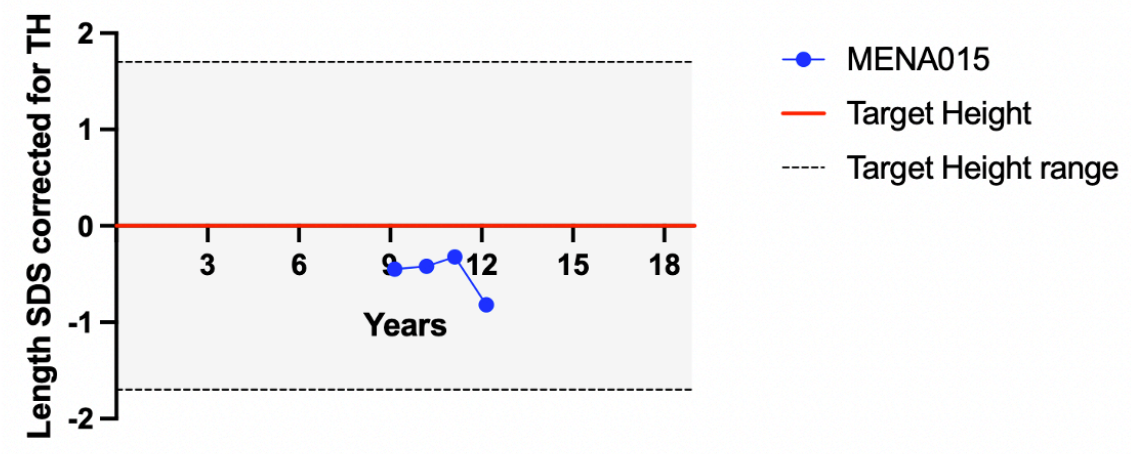
5]


Length SDS corrected for TH
2
1
0
-1
-2
3
6
9
12
15
18
Years
MENA011
Target Height
Target Height range
pHPT
Surgery (MIA)
Surgery

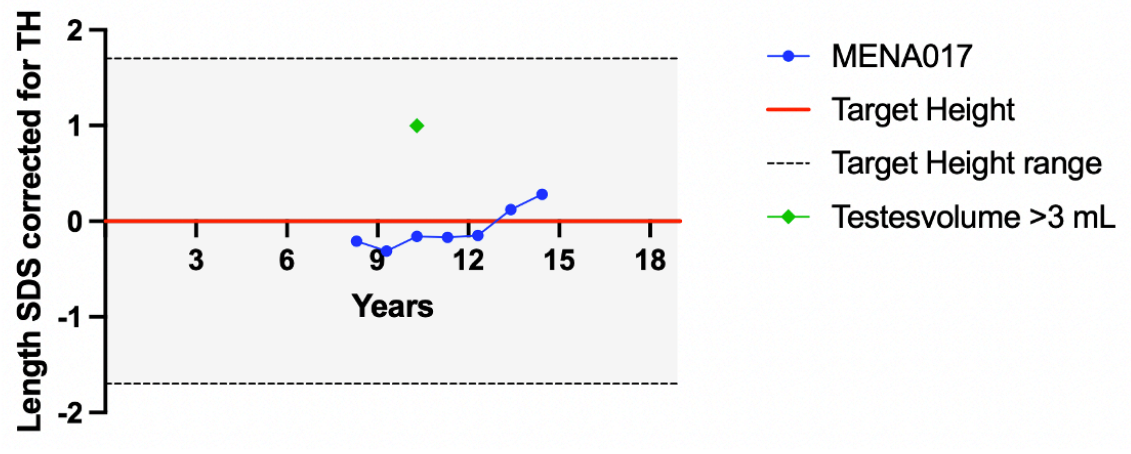
6]


Length SDS corrected for TH
3
2
1
0
-1
-2
3
6
9
12
15
18
Years
MENA013
Target Height
Target Height range

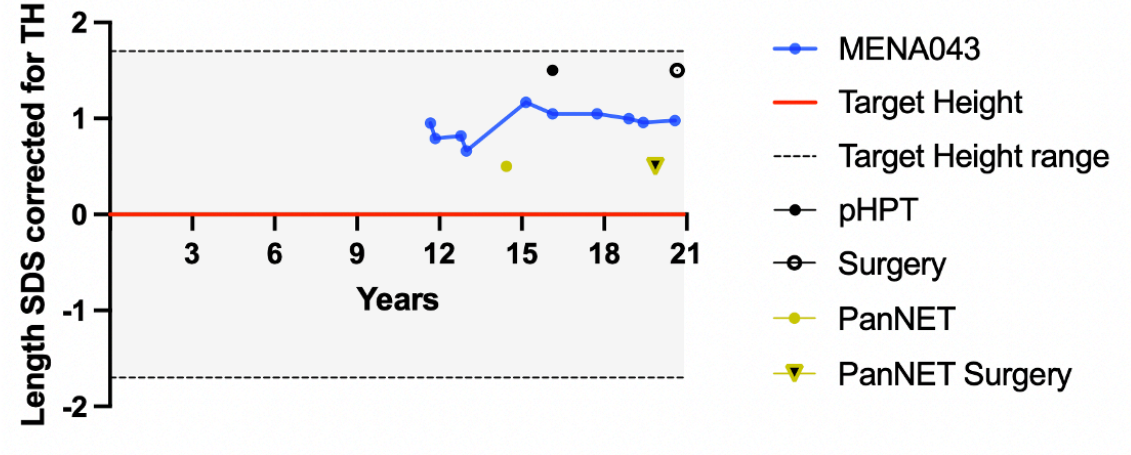
7]


Length SDS corrected for TH
2
1
0
-1
-2
3
6
9
12
15
18
Years
MENA015
Target Height
Target Height range

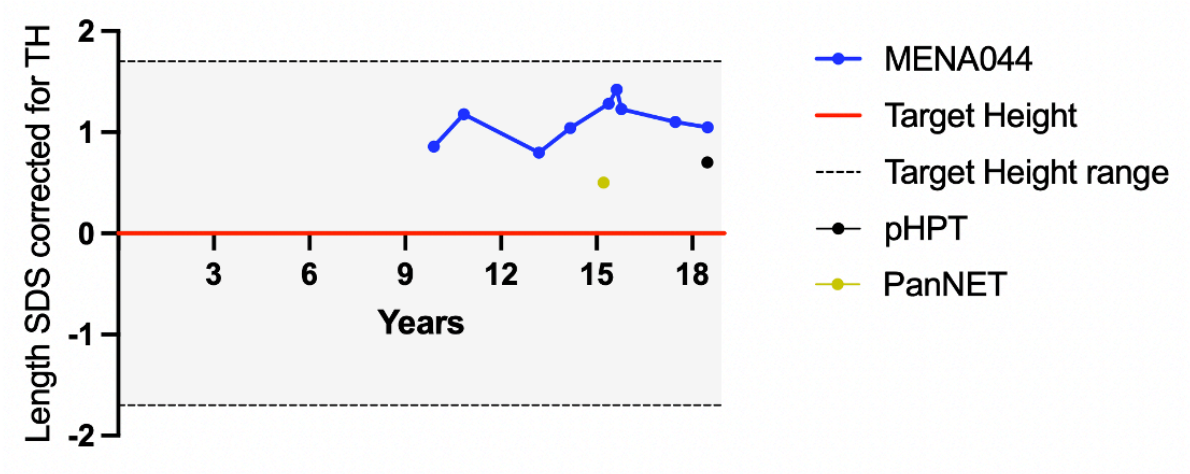
8]


Length SDS corrected for TH
2
1
0
-1
-2
3
6
9
12
15
18
Years
MENA017
Target Height
Target Height range
Testesvolume >3 mL

9]


Length SDS corrected for TH
2
1
0
-1
-2
3
6
9
12
15
18
21
Years
MENA043
Target Height
Target Height range
pHPT
Surgery
PanNET
PanNET Surgery

10]



11]

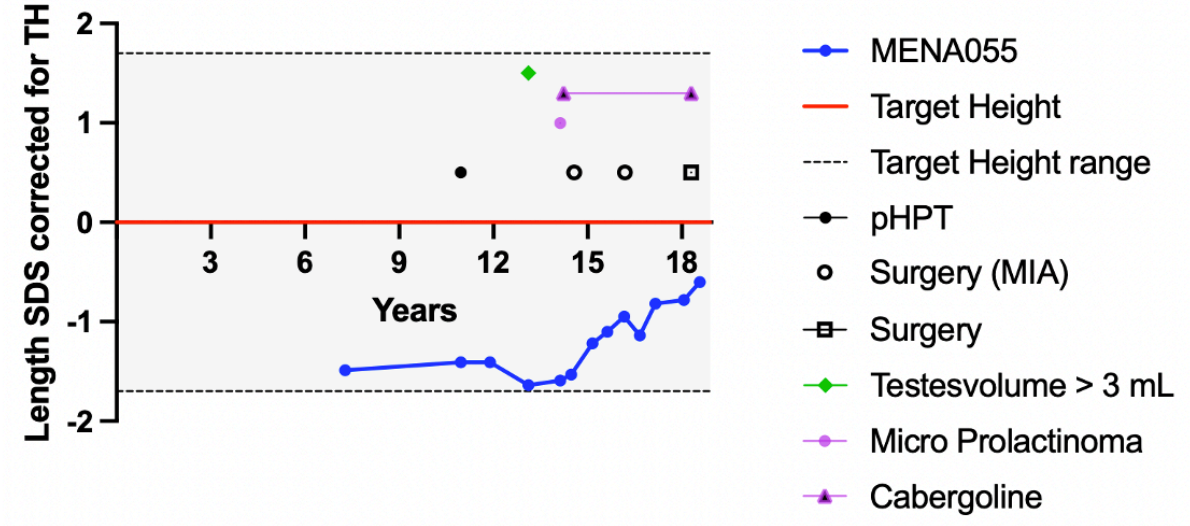


Figure 4. **B. 1] - 11]** Plots of each male patient with known growth/pubertal data, manifestations and intervention. Blue line = length SDS corrected for TH of patient, red line = target height. pHPT = primary hyperparathyroidism, PanNET = pancreatic neuroendocrine tumor, M2 = Mammae 2 (Tanner stages), MIA = minimal invasive adenomectomy.