CLINICAL STUDY

The appearance of the adrenal glands on computed tomography in multiple endocrine neoplasia type 1

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Abstract

Aims: To review the morphology of the adrenal glands in multiple endocrine neoplasia type 1 (MEN1) on computed tomography (CT) to compare the results with established normal values for adrenal size and nodularity and to correlate adrenal size with serum cortisol secretory dynamics.

Materials and methods: Two observers independently reviewed the adrenal CT in 28 patients with MEN1, measuring the maximum width of the body of the gland and the medial and lateral limbs. Incidence and location of nodules > 5 mm within the gland were recorded. Following exclusion of known cases of Cushing's syndrome, adrenal gland size was compared with previously documented normative data. Adrenal gland size was compared between patients with normal and abnormal cortisol dynamics.

Results: Comparison of mean adrenal size in MEN1 patients with normative data showed that the adrenal limbs were significantly larger in MEN1 than normal ($P < 0.0001$ in all four limbs). Adrenal body was also significantly larger ($P < 0.05$). Nodules were demonstrated in 17 (60%) of patients (versus 0.4–2% in the normal population). No statistically significant correlation was demonstrated between adrenal limb hyperplasia and abnormal cortisol dynamics.

Conclusions: In patients with MEN1, adrenal limb hyperplasia and adrenal nodules are significantly more common than in the normal population, a phenomenon not previously documented in a quantitative manner. There was no significant correlation between adrenal limb hyperplasia and abnormal cortisol dynamics.

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an inherited, autosomal dominant cancer syndrome. Tumours classically described in MEN1 are neoplasia of the anterior pituitary, parathyroid glands and endocrine pancreas but other neuroendocrine tumours, lipomas and ependymomas are also seen (1). MEN1 gene has been located on chromosome 11q13 and encodes for a nuclear protein called menin that is thought to have a tumour suppressor function (2).

Although observational studies have reported adrenal abnormalities in 30–40% of MEN1 patients including hyperplasia, nodularity and neoplasia, the exact frequencies and nature of the abnormalities have not been fully documented. Where hyperplasia is suspected, measurements have not been performed, nor have the size of the glands been compared with normal values, making the changes arbitrary (3, 4). Interestingly, those benign adrenal lesions that have

been studied do not show inactivation of the remaining non-mutated menin gene, suggesting that they do not fit a classical two-hit theory of neoplasia (4). Initial reports that adrenal lesions are found only in patients with pancreatic hypersecretion have not subsequently been proven (5).

In this study, we reviewed the computed tomography (CT) imaging of the adrenal glands in a cohort of patients with MEN1, comparing the size of their adrenals with established normal values for adrenal size, as described by Vincent *et al.* (6). Modern CT is now capable of identifying small nodules, often less than 5mm. We have documented the presence, number and size of any adrenal nodules and compared these findings with those described in the normal population (7). The majority of adrenal lesions in MEN1 have previously been reported to be non-functioning (3, 8, 9). We reviewed the patients' serum cortisol secretory dynamics and sought potential correlations with adrenal morphology.

Methods

Patients and endocrine investigation

The diagnosis of MEN1 was made either by genetic confirmation or a positive family history with two or more typical endocrine lesions. The diagnoses of classical MEN1 lesions were made using the following modalities: MRI pituitary with standard anterior pituitary function testing, serum PTH and calcium in conjunction with ultrasound and sestamibi radionuclide parathyroid localisation and CT scanning of the abdomen with fasting gut peptides for detection of islet cell tumours. In total, 37 patients fulfilled this criterion. Abdominal CT imaging was available in 28 patients with confirmed MEN1; biochemical data were accessible for 21 of these patients. Three patients with known pituitary dependent Cushing's were excluded from the adrenal size analyses due to the predictability of adrenal gland enlargement and abnormal cortisol dynamics. One patient with bilateral adrenal macronodular hyperplasia was similarly excluded.

Low-dose dexamethasone suppression test (LDDST; dexamethasone 0.5 mg orally 6 hourly for 48 h) and/or midnight serum cortisol (asleep) results were obtained from a retrospective case notes study and by recalling (where possible) and performing LDDST in patients with

no prior results. Normal results were defined as a cortisol level of < 50 nmol/l for both tests. Where more than one result was available, the lowest reliable (asleep) midnight cortisol was used. Where only unreliable (awake) midnight cortisol results were available the result of the LDDST was used. Table 1 shows the demographics and clinical diagnoses of the cohort studied.

Imaging technique

CT was available on all 37 patients, however, electronic CT data, suitable for measurement and detailed analysis, was available in only 28 patients, and these formed the cohort for study. These 28 patients were scanned for various clinical indications, including assessment and screening for pancreatic and adrenal neoplasia and liver metastases. In patients in whom more than one CT examination had been performed, the scan closest to the time of diagnosis was studied. The scans dated from 1992 to 2004 and were performed on GE Lightspeed Ultra, GE Hispeed ZXi and GE Hispeed Advantage RP CT scanners (General Electric, Waukesha, WI, USA). Contiguous slice thickness varied between patients; 17 patients at 5 mm, 9 patients at 3 mm, 2 patients at 3.5 mm and 1 patient at 10 mm. In all patients contrast medium was injected intravenously.

Table 1 Clinical features and serum cortisol dynamics of MEN1 patients.

Patient numbers	Gender/age	Diagnoses	Cortisol (nmol/l)	
			LDDST	Midnight cortisol
1	M 42	PTH, Gastric Carcinoid	/	< 50 asleep
2	F 46	PTH, PRL	< 20	/
3	F 60	PTH, Pituitary Cushing's	< 50	64 awake
4	F 50	PTH, Gastrinoma, Insulinoma	< 20	/
5	F 35	PTH, PRL, islet cell tumour	/	/
6	F 72	No data available	/	/
7	F 46	PTH, bronchial carcinoid	< 50	68 asleep
8	M 67	PTH, gastrinoma, thymic carcinoid	85	/
9	F 40	PTH, NFPA	/	< 20 asleep
10	M 48	PTH, NFPA, islet cell tumour	/	/
11	F 64	PTH, acromegaly, carcinoid	/	< 50 asleep
12	M 59	PTH, acromegaly	< 20	/
13	F 52	PTH, NFPA, glucagonoma	< 50	< 50 asleep
14	F 66	Insulinoma, Pituitary Cushing's	/	250 asleep*
15	F 55	PTH, insulinoma, thymic carcinoid	589	460 asleep**
16	F 52	PTH, gastrinoma, NFPA	< 50	95 awake
17	M 49	PTH, NFPA, islet cell tumour	/	31 asleep
18	M 60	PTH, NFPA, insulinoma, gastrinoma	/	63 asleep
19	F 87	PTH, insulinoma	/	/
20	M 57	PTH, insulinoma, gastrinoma	/	80 asleep
21	M 74	PTH, PRL, gastrinoma	313	80 asleep
22	M 53	PTH	21	/
23	F 46	PTH, gastrinoma	< 50	177 asleep
24	F 87	No data available	/	/
25	M 66	PTH, acromegaly, gastrinoma	< 50	/
26	F 53	PTH, NFPA, gastrinoma	< 50	72 asleep
27	M 88	No data available	/	/
28	F 75	PTH, Pituitary Cushing's	/	/*

Cortisol dynamics are determined by nadir serum cortisol on low-dose dexamethasone suppression test and/or midnight serum cortisol. Normality of cortisol secretion is demonstrated by a sleeping midnight cortisol result of < 50 nmol/l and/or a nadir serum cortisol of < 50 nmol/l on low-dose dexamethasone suppression test. *denotes patient with known pituitary dependent Cushing's syndrome, **denotes patient with bilateral macronodular adrenal hyperplasia.

Image interpretation

The images were reviewed on a remote console and interpreted by two radiologists experienced at adrenal imaging (AGR and RHR). Initially, two scans were reviewed together by the observers to ensure similar measurements were undertaken. The remaining scans were then reviewed by the observers independently with nine of these scans reviewed by both in order to calculate inter-observer variability. Measurements were made according to previously published methodology (6, 10). These included: the maximum width perpendicular to the long axis of the gland and the maximum width of the medial and lateral limbs. The presence of nodules over 5 mm and their size was recorded.

Statistical analysis

The data obtained were entered into an Excel spreadsheet. Data distribution were skewed due to the presence of bilateral autonomous macronodular hyperplasia; exclusion of this case resulted in a normal distribution. An unpaired *t*-test was used to compare the adrenal body and limb size in the MEN1 cohort with previously published normative data from Vincent *et al.* Inter-rater reliability was calculated for the patients for whom measurement overlapped between observers. Comparison of adrenal body and limb measurements between the normal and abnormal cortisol dynamic group was performed using an unpaired *t*-test.

Results

Size of gland

The average measurements and range of measurements for the right and left adrenal glands in our MEN1 cohort are shown in Table 2. Following exclusion of patients with known Cushing's syndrome, comparison was made with previously published normative data from Vincent *et al.* The adrenal limbs were significantly larger in the MEN1 cohort compared with the normal population

($P < 0.0001$ in all four limbs). The body was also significantly larger ($P = 0.0158$ and 0.0490). Furthermore, 7 out of the 24 patients had all four limbs more than 2 s.d. above the normal mean, 11 out of the 24 had at least three limbs more than 2 s.d. above the normal mean and 20 out of the 24 patients had at least one limb larger than 2 s.d. above normal mean (Table 3).

Inter-rater reliability

Of the 28 patients with MEN1, two were measured by RHR and AGR together, nine others measured independently by both RHR and AGR, seven others measured by AGR alone, ten others by RHR alone. For the nine patients with independent measurements by two observers the correlation between the observations was measured. Each patient yields six values and using a one-tailed test; five out of the six tests yielded a significant positive correlation (Table 4). As Table 4 shows, only the left lateral measurement indicated a poor correlation between the two observers. However, the average difference between observers in this group of nine patients was only 0.8 mm, so agreement between observers was thought to be acceptable.

Nodularity, percentage of adrenals with nodules

In 17 out of the 27 (60%) patients one or more adrenal nodule over the size of 5 mm was found, three patients had a nodule or nodules that were greater than 10 mm, while the rest were between 5 and 10 mm. This compares with 0.4–2% in the normal population (7). The nodules were predominantly focal (88%) rather than multiple (12%) (Fig. 1).

Adrenocortical function

The patients were grouped according to whether they had normal or abnormal serum cortisol dynamics according to the LDDST and midnight cortisol results. Normal

Table 2 Mean adrenal gland measurements for the MEN1 and normal populations.

Adrenal position	MEN1 (mm)			Normal (mm)			Difference between MEN1 & normal (mm)			
	N	Mean (S.D.)	S.E.M.	N	Mean (S.D.)	S.E.M.	Mean	t	df	P-value
Body										
Right	24	7.45 (2.71)	0.89	55	6.1 (2)	0.27	1.350	2.468	77	0.0158
Left	24	9.11 (3.18)	1.04	55	7.9 (2.1)	0.28	1.210	2.000	77	0.0490
Medial										
Right	24	4.65 (1.51)	0.45	50	2.8 (0.8)	0.11	1.850	6.905	72	<0.0001
Left	24	5.29 (1.73)	0.79	34	3.3 (0.9)	0.15	1.990	5.714	56	<0.0001
Lateral										
Right	24	4.92 (1.60)	0.49	38	2.8 (0.6)	0.10	2.120	7.412	60	<0.0001
Left	24	4.98 (1.59)	0.67	42	3.0 (0.1)	0.02	1.491	8.090	64	<0.0001

This table shows the means of the sizes of the individual bodies and limbs of the adrenals in the MEN1 and normal population with comparison using an unpaired *t*-test.

Table 3 Frequency of adrenal measurements > 2 s.d. above mean of normal population.

	N	Frequency of limbs > 2 s.d.
Body		
Right	24	3 (12.5%)
Left	24	4 (16.6%)
Medial		
Right	24	12 (50%)
Left	24	12 (50%)
Lateral		
Right	24	11 (45.8%)
Left	24	18 (75%)

This table demonstrates the comparison of the adrenal size of the MEN1 cohort with a normal population (from Vincent *et al.*). This demonstrates the prevalence of adrenal limb size >2 s.d. above the mean of a normal population.

cortisol dynamics are defined as a serum cortisol of < 50 nmol/l for both tests. Where available, accurately measured asleep midnight cortisol results have been used in preference to the low-dose dexamethasone suppression test; a sleeping midnight cortisol result of < 50 nmol/l excludes abnormal cortisol secretory dynamics (Table 5). Cushing’s disease was diagnosed on the basis of abnormal serum cortisol secretion combined with a diagnostic central to peripheral gradient on bilateral simultaneous inferior petrosal sinus sampling, as previously described (11). There was no statistically significant correlation between adrenal limb hyperplasia and abnormal cortisol dynamics (Table 5).

Discussion

In this retrospective review, we have for the first time directly measured the size of the adrenal glands in patients with MEN1 using electronic callipers and established methodology (6). This methodology has been used repeatedly in other studies (12–14). The methodology was confirmed within the study by showing that two independent observers had inter-observer variability

Table 4 Inter-rater reliability.

	r	P	N
Body			
Right	0.64	0.031	9
Left	0.63	0.034	9
Medial			
Right	0.66	0.026	9
Left	0.87	0.00103	9
Lateral			
Right	0.78	0.012	8
Left	0.23	0.272	9

The adrenal size of nine patients was assessed independently by two observers and the correlation was measured; five out of six tests yielded a positive correlation. Despite the lack of correlation for the left lateral measurement, the average difference between observers in the left lateral measurement was only 0.8 mm.

Figure 1 Contrast enhanced axial CT images of the adrenal glands. (a) 41-year-old female patient with MEN1 demonstrates a 1 cm nodule arising from the lateral limb of the left adrenal (black arrow). (b) 46-year-old male patient with MEN1 demonstrates small 0.8 cm nodule arising from lateral limb of the right adrenal (black arrow). A pancreatic cyst is also present (black arrowhead). (c) Normal sized adrenal glands for comparison.

within an acceptable range. We have also for the first time in MEN1 compared the results of the measurements to established normal values (6).

Our results show that the adrenal limbs in patients with MEN1 are significantly larger than the adrenal limbs in a normal population. To a lesser extent, a difference was also detected in adrenal body size. Dobbie and Symington (15) showed that the limbs of the adrenal gland consist predominantly of adrenal cortical tissue with little or no medullary tissue, which is maximal in the body. Enlargement of the limbs indicates adrenal cortical expansion and our study therefore confirms previous reports that adrenocortical hyperplasia is part of the MEN1 syndrome. Overall, the mean thickness of the adrenal limbs in MEN1 is significantly larger than that of the normal population. More significantly, 20 out of the 24 (83%) had at least one limb 2 s.d. larger than the normal mean, while 7 out of the 24 (29%) had all four limbs more than 2 s.d. larger. There were no

Table 5 Mean size of adrenals according to the serum cortisol secretory dynamics.

		Normal cortisol dynamics <i>n</i> =12			Abnormal cortisol dynamics <i>n</i> =7			<i>P</i> value
		Mean	S.D.	S.E.M.	Mean	S.D.	S.E.M.	
Body width (mm)	Right	5.82	2.29	0.66	8.45	1.48	0.56	0.015
	Left	7.63	3.69	1.06	10.30	2.02	0.76	0.098
Medial limb (mm)	Right	4.02	1.41	0.41	4.86	0.94	0.35	0.178
	Left	4.43	1.55	0.45	5.76	1.21	0.45	0.069
Lateral limb (mm)	Right	4.24	1.43	0.41	5.14	0.92	0.35	0.156
	Left	4.48	1.16	0.33	5.51	1.41	0.53	0.102

The adrenal size was compared between the groups of patients with normal versus abnormal cortisol secretory dynamics, as determined by midnight cortisol or low-dose dexamethasone suppression test. Patients with known Cushing's syndrome were excluded from the comparison. The adrenal size was compared using an unpaired *t*-test.

distinguishing clinical features of the four patients who lacked adrenal hyperplasia, all had hyperparathyroidism, three had pituitary tumours and three had pancreatic endocrine tumours. A previous study by Skogseid *et al.* (16) suggested that adrenal enlargement was associated with the presence of pancreatic endocrine tumours. This does not appear to be evident within our cohort; three out of four with normal adrenal size and 7 out of 24 with adrenal hyperplasia had confirmed pancreatic endocrine tumours.

There was no statistically significant correlation between adrenal hyperplasia and abnormal cortisol dynamics, although we note our small sample size. The association of adrenal limb hyperplasia with MEN1 does pose the question as to whether MEN1 patients should be routinely assessed for abnormal cortisol dynamics. Chronic, autonomous cortisol production may be associated with hypertension, hyperlipidaemia, insulin resistance and osteopenia, without necessarily the development of overt Cushing's syndrome (17). A variety of methods may be used to assess cortisol status as demonstrated in this study, including standard low-dose or overnight dexamethasone suppression tests and the assessment of circadian rhythm with midnight cortisol measurements.

The relative rarity of MEN1 inevitably reduces the numbers of patients available for a study such as this. Furthermore, we acknowledge that the retrospective nature of the study will necessarily introduce an element of bias with regard to availability of relevant data. However, notwithstanding these caveats, our study shows that in patients with MEN1, adrenal limb hyperplasia and adrenal nodules are significantly more common than in the normal population; a phenomenon not previously documented with precise quantitation.

However, in this small series there was no statistically significant correlation between adrenal limb hyperplasia and abnormal cortisol dynamics.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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