Prevalence and Characteristics of Adrenal Tumors and Myelolipomas in Congenital Adrenal Hyperplasia: A Systematic Review and Meta-Analysis

Journal:	<i>AACE Journals</i>
Manuscript ID	Draft
Manuscript Type:	EP - Review Article
Keywords:	Adrenal Hyperplasia, Congenital, Adrenogenital Syndrome, Adrenal, Adrenal Gland Diseases

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**Prevalence and Characteristics of Adrenal Tumors and Myelolipomas in
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For Review Only

ABSTRACT

Context: The prevalence of adrenal tumors in congenital adrenal hyperplasia (CAH) is uncertain.

Objective: To estimate the prevalence and characteristics of adrenal tumors and myelolipoma in CAH, and investigate clinical features of this population.

Data Sources Methods: Systematically searches in Medline Ovid and Embase for articles published until January 2020.

Study Selection: Studies with confirmed CAH, biochemically and/or genetically, were included.

Data Extraction: The two authors independently extracted data from each study.

Results: Six cohort studies were included in the prevalence calculation. In addition, 32 case reports on adrenal myelolipomas and CAH were included. The prevalence of adrenal tumors in CAH was 29.3%. When only studies with genetically verified *CYP21A2* mutations were included the prevalence was 23.6%. The prevalence of myelolipoma in CAH was 7.4% (verified *CYP21A2* mutations 8.6%). The proportion of myelolipoma in the adrenal tumors was 25.4% (genetically verified 36.6%). The median (range) age at tumor diagnosis was 36.0 (12-60) years and there were more tumors in males than in females (37.9% vs. 22.1%, $P<0.05$). In patients with myelolipomas 95.7% had an undiagnosed or poorly managed CAH.

Conclusion: Patients with CAH had a high prevalence of adrenal tumors, particularly myelolipoma. Those with myelolipomas had a high frequency of late diagnosed or poorly controlled CAH. Adrenal imaging may be considered in patients with CAH, especially if abdominal pain is present.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder with impaired synthesis of adrenal glucocorticoids with impaired cortisol and aldosterone production. Mutations in the *CYP21A2* gene result in 21-hydroxylase deficiency (21OHD) which is by far the most common variant of CAH (95-99%) (1, 2).

CAH is divided into classical, which includes the salt-wasting (SW) and simple virilizing (SV) forms, and the nonclassical form (NC). Other less common variants are 11 β 1-hydroxylase deficiency (3), 3 β -hydroxysteroid dehydrogenase deficiency (4) and 17 α -hydroxylase deficiency (5), but more uncommon variants exists as well (6, 7). Almost all CAH variants will result in increased ACTH production from the pituitary gland due to negative feedback from the adrenals. In most CAH variants, including 21OHD, ACTH stimulates increased androgen production from the adrenals causing virilization in affected girls but also in male toddlers with SV if no neonatal screening has been done (8). ACTH is also a growth factor to the adrenals enhancing adrenal growth with large adrenals, hyperplasia, in CAH when untreated. Whether ACTH hypersecretion also cause tumor growth is uncertain. Few studies have systematic investigated the adrenals radiologically in patients with CAH (9, 10), and routine screening for adrenal masses in CAH are not recommended (11). One study found increased frequency of adrenal adenoma in 11% of patients with CAH (10), particularly adrenal myelolipomas, while an older study found an even higher frequency (83%)(9).

Myelolipomas are benign tumors of the adrenal cortex with adrenal, adipose and myeloid components (12). They are often hormonal inactive and were previously considered to be rare. However, the reported number of myelolipomas in patients with CAH has increased during the last years, probably due to the increased use of abdominal imaging. With this increased

use of abdominal imaging adrenal tumors in general also have been found to be common in the elderly with a prevalence of up to 15% (13), but much lower in the younger population, especially below 40-years of age. The majority are benign adrenal adenomas with no hormone excess production (14). One meta-analysis estimated a prevalence of biochemically diagnosed CAH in incidentalomas to 5.9%, however, it was reduced to only 0.8% when only patients with genetically verified CAH were included (15). Screening for CAH with 17-hydroxyprogesterone (17OHP) has been recommended in patients with bilateral adrenal incidentalomas (16).

The aim of this systematic review and meta-analysis was to investigate the prevalence of adrenal tumors in CAH with a special focus on myelolipomas. We also wanted to characterize the patients with CAH and concurrent adrenal tumor as well as investigate if there is evidence to recommend regular adrenal imaging in the follow-up of CAH.

Methods

Search Strategy

All studies published on the topic adrenal tumors and CAH was included with no restriction on age or language. Meeting abstracts were excluded but case reports about CAH and adrenal tumors was included. Systematic searches were performed using Medline Ovid from 1984 and Embase until 31 December 2019 using the following search strategy “(adrenal adj3 (cancer* or neoplasm* or tumor* or tumour* or incidentaloma* or nodule* or pheochromocytoma* or mass or masses or myelolipoma* or cushing)).mp”, “conn adenoma*. Mp”, “primary hyperaldosteronism. Mp or Hyperaldosteronism/” in search one and “congenital adrenal hyperplasia.mp”, “21-hydroxylase deficiency.mp”, “*CYP 21A2*. Mp”, “11-hydroxylase deficiency.mp”, “3 beta hydroxysteroid dehydrogenase deficiency. mp” and “17-alfa

hydroxylase deficiency.mp” in search two. Then each theme in search one was combined with each theme in search two and duplicates were removed. Searches specified with .mp searches multiple fields, such as title, abstract, subject headings and keywords, while * means truncation, i.e., retrieves all possible suffix variations of the root word indicated and adj3 means that the search words must appear maximum three words apart. Articles were considered by reviewing the title, then the abstract, and the full text if in doubt.

Selection criteria

The inclusion criteria was a confirmed CAH diagnosis, e.g. 21-hydroxylase deficiency was verified with high 17-hydroxyprogesterone (17OHP) $\geq 30\text{nmol/L}$ and/or *CYP21A2* mutations and/or had a typical clinical presentation of CAH (17). If the same group had presented several studies, we only included the patients once. We also identified other types of CAH than 21OHD with myelolipoma. Both authors did the literature search independently and a university librarian helped with the search. Disagreements were solved by consensus.

A quality assessment of the studies of CAH and adrenal tumors was incorporated with our comments on the strength and limitations by free text. No formal quality assessment tool was used since none has been developed to study prevalence or case reports. The PRISMA guidelines were followed (18).

Data extraction

The two authors independently extracted data from each study. The following information was recorded from each study: first author, publication year, country, title, number of patients with CAH and tumors, CAH variant and diagnostic criteria for the CAH diagnosis.

From the individual cases we extracted: gender, age at adrenal tumor diagnosis and CAH diagnosis, CAH variant, 17OHP values, genetic analyses, tumor classification, largest diameter of the tumor, tumor side and/or if bilateral and treatment. If data was missing the corresponding author of the studies was contacted.

Statistical Analysis

Results were calculated after merging data from all studies. In the meta-analysis the results were given as median and range. Pearson's Chi square test was used to compare the prevalence of adenoma in men and woman and side of tumor and to compare the prevalence of myelolipoma in the patients and the normal population. The prevalence of myelolipoma at age 40 in the normal population was calculated to 0.32% (8% of the adrenal adenoma which have a prevalence of 4%) (19). To compare continues variables *t*-test were used while Chi square or Fischer Exact test were used for categorical variables. Statistical significance was accepted for $P < 0.05$.

Results

The Medline Ovid and Embase searches identified 676 publications, of which 195 were duplicates. Forty-seven publications were considered eligible for inclusion. Only seven of these studies investigated the prevalence of adrenal tumors in CAH (9, 10, 20-24). Two of them reported on the same patient cohort (9, 20) so only the most recent study was used in the meta-analysis (9). These six cohort studies included 215 patients and 63 of them had an adrenal tumor. Three of the studies (9, 22, 24) had defined an adrenal mass $\geq 5\text{mm}$ but we also extracted data on tumors $\geq 10\text{mm}$. The other 38 papers were case reports with adrenal

myelolipoma and CAH, including 42 cases with 21OHD (10, 22, 25-63). We identified 10 cases with other types of CAH than 21OHD with myelolipoma. These cases were not included in the analysis due to low numbers; nine had 17 α -hydroxylase deficiency (59, 64-69) and one 11 β - dehydrogenase deficiency (70). For the same reason four case reports with adrenal cortical cancer and 21OHD also were excluded (71-74). A fifth case with cortical cancer and CAH was published autumn 2019 and was a mixed tumor with myelolipoma and included in Table 3 (63).

Figure 1 shows the flow diagram for the searches. Table 1 reports the main characteristic for the six studies with the prevalence of adrenal tumors in CAH. Three of these studies had also included five patients with other enzyme deficiencies than 21OHD. Four of these five patients (75%) with other enzyme deficiencies than 21OHD had an adrenal tumor.

Meta-Analysis

The prevalence of adrenal tumors (≥ 5 and ≥ 10 mm, respectively) in CAH was 29.3% (19.5%) and in 21OHD 28.4% (18.3%). When only studies with verified *CYP21A2* mutations were included the prevalence was 23.6% (16.7%)(Table 1). The prevalence of myelolipoma in CAH was 7.4% and in patients with verified *CYP21A2* mutations 8.2%. The prevalence of myelolipoma when including only the two largest studies with unselected patients with CAH(10, 22) was 10.1% (15 of 148), 95% CI [5.3-15.0], diagnosed at age 40 (19-65) years. This is significant higher than the estimated frequency of myelolipoma in the normal population of 40 years which is estimated to 0.32%, 95% CI [-1.3-1.7].

The proportion of myelolipoma in the adrenal tumors was 25.4% and raised to 36.6% when only the studies with verified *CYP21A2* mutations were included (Table 1). A pheochromocytoma with a diameter 165 mm (10) and another of 28 mm (22) were reported in two separate studies. The other cohort studies only reported the type of tumor if the patient

had a large tumor and had had an adrenalectomy (9, 21). No other etiology than benign adenoma, hyperplasia or myelolipoma were reported in these studies. The median age at tumor diagnosis was 38.0 (12-62) years and there were more tumors in males than in females 37.9% vs. 22.1%, $P < 0.05$ (Table 2). Tumors were equally frequently reported in the SW as the SV phenotype (40.9% vs 45.5%, $P > 0.5$). Five of the studies had data on whether the tumors were bilateral or not and of these 22.7% reported bilateralism. Most tumors were found on the left side (56.8%). Nermoen et al. (10) and El-Maoche et al. (22) had not published information on tumor side but data were provided after contact with the corresponding authors. The median diameter of the tumors was 24.0 (4-165) mm (Table 2). Four of the studies used computed tomography (CT) and two magnetic resonance imaging (MR)(Table 2).

Data on myelolipoma and CAH was from 42 case reports with 21OHD (25-61) and 15 cases from two of the prevalence studies (10, 22)(Table 3). The case with myelolipoma in the article by Jaresch et al.(9) was not included due to missing data. Nermoen et al. had published data on one patient in two publications but we included the patient only once (10, 43). Of the 57 cases with 21OHD and concomitant myelolipoma 46% were asymptomatic and 33% had abdominal or flank pain (Table 3). Compared to CAH patients with adrenal adenoma the CAH patients with myelolipoma were older (44 vs 33 years, $P < 0.05$), had larger tumors (102 vs 10 mm, $P < 0.005$), were more often bilateral (59.6% vs 10.7%, $P < 0.05$) and occurred more often in men, however, this was not significant (66.7% vs 35.7% $P = 0.3$). Almost all patients with myelolipoma had a late diagnosed or poorly managed CAH (95.7%).

Discussion

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This is the first systematic review and meta-analysis of the prevalence of adrenal tumors in CAH. We found a high prevalence of adenomas and myelolipomas in this young population of mainly 21OHD and adrenal imaging in patients with CAH may be considered.

An increasing number of case reports of CAH with myelolipoma have been published the last few years. We found that the CAH patients have more than 30 times (10.1% vs 0.32%) increased risk of having myelolipoma compared to the general population. Does it have any clinical relevance to diagnose a myeloma in a CAH patient? Myelolipomas are benign slow growing tumors that often have been interpreted as malignant and the patients have been adrenalectomized unnecessarily (9). Even if the tumors is above 4 cm it need not to be removed. To avoid this, it is important that both the patients and the clinicians are aware of whether a myelolipoma is present or not. The diagnosis is normally done by the characteristic radiological appearance with round, sharp-demarcated lesion with presence of fatty foci with attenuation values between -30HU to -100HU (75). However, very large myelolipomas have an increased risk of hemorrhage and elective removal could be considered if they exceed 10 cm (76). Therefore, we suggest that CAH may be considered in every patient with a myelolipoma. In the review by Decmann et al. 10% of patients with myelolipoma had concurrent CAH (12).

It is well known that increased ACTH levels act as a growth factor on adrenal cells resulting in large adrenals. Whether ACTH hypersecretion also cause tumor growth is uncertain, but may be one reason for the high frequency of myelolipomas and adenomas in CAH. However, the etiology of myelolipoma growth is largely unknown, and it has been proposed that development from residual embryonic mesenchymal tissue in the adrenal glands, or metaplasia of reticuloendothelial cells, is a result of chronic stress (76). It has also been postulated that ACTH elevation might induce transformation of adrenal tissue into myeloid

tissue (77). At least two case reports have investigated steroid receptors in myelolipomas.

Hagiwara et al. did not find overexpression of ACTH or androgen receptors in a giant myelolipoma in a woman with CAH (42). However, Almeida et al. detected increased expression of ACTH (Melanocortin 2 receptor) and androgen receptors in giant bilateral myelolipomas from patients with CAH. This systematic review and meta-analysis support the theory that chronic ACTH stimulation could have a direct role in the development of adrenal lesions, especially myelolipomas.

The data for the meta-analysis were somewhat limited since only six studies had investigated the frequency of adrenal tumors in CAH, and only two of them had a larger study population with 63 and 88 participants, respectively (10, 22), compared to 4-26 participants in the other studies (9, 21, 23, 24). However this is the best information we have to date on this rare disease and prevalence of adrenal adenoma. The meta-analysis showed that 28.1% of patients with 21OHD had at least one adrenal tumor, and when including only those with genetically verified 21OHD the prevalence fell slightly to 23.2%. Jaresch et al. found a very high prevalence of adrenal tumors of 80% (9), by examining 22 CAH patients with CT and defining an adrenal mass over 5 mm as a tumor. Half of the tumors were only 5-9 mm and thus macronodular hyperplasia may have been interpreted as adrenal tumors. If Jaresch et al. had defined an adrenal tumor as ≥ 10 mm the prevalence would still be high at 40.9% (Table 1).

Normally lesions of 10 mm in size or more are defined as adrenal tumors (78). However, both Reisch et al. and El-Maouche et al. (22, 24) defined a mass over 5 mm as a tumor. We obtained additional information from the authors of the exact numbers of tumors ≥ 10 mm and still the prevalence of adrenal tumors in CAH was considerable higher than reported in the general population. The prevalence in the general population of silent adrenal adenomas has

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been estimated to <1% in the young, 2-4% in the middle ages (50s) and more than 10% in the elderly (13). The median age in the CAH group was 36 year when the tumors were diagnosed and with a prevalence of 16.5% (adenoma size ≥ 10 mm) there was at least a five-fold increase compared to the general population. Moreover, a large proportion of the adrenal tumor in CAH were myelolipomas. Reisch et al. used MRI, and did not report any myelolipomas in their study (24). However, the applied technique did not include fat suppression imaging which could have discriminated myelolipomas from adenomas. In addition, Jaresch et al. used CT and the only myelolipoma they reported was first diagnosed after adrenalectomy due to size and only mentioned in the discussion (9). Furthermore, we have seen several unpublished case reports being presented at different meeting the last few years. We therefore postulate that the proportion of myelolipomas in 21OHD may be underestimated. We suggest that in the follow-up of the adult patients with CAH an imaging of the adrenals may be considered once in adulthood and perhaps regularly every five to ten year depending on the result of the imaging. Especially if abdominal pain is present imaging could be considered since many of the myelolipomas presented with abdominal pain. CT should be considered as the first radiological investigation since MRI do not detect small calcifications that myelolipoma may demonstrate. It is also recommended to use noncontrast CT in all adrenal tumors to determine if the mass is homogenous and lipid-rich and therefore benign (16). An adrenal mass is considered benign when the HU are ≤ 10 and the tumor is homogenous and smaller than 4 cm, then no further imaging is required (16). Ultrasound is not a good screening method if the adrenal tumors are small since they are located deep within the abdomen and surrounded by fat (75). However, in the follow-up of a large myelolipoma or adenoma ultrasound or MRI could be the preferred imaging to avoid unnecessary ionizing radiation. In the case reports with myelolipoma near all the patients had a poorly treated or late diagnosed CAH with high ACTH –levels and optimization of the

glucocorticoid replacement is warranted. If the patient has undiagnosed CAH with glucocorticoid and/or mineralocorticoid deficiency surgery could be fatal due to the risk of developing an adrenal crisis per- or postoperative (79, 80).

Conclusion

Patients with CAH had a considerable higher prevalence of adrenal tumors, particularly myelolipomas, compared to the general population and at a younger age. In addition, almost all patients with CAH and concurrent myelolipoma had late diagnosed or poorly controlled CAH. Physicians and the patients should be aware of the increased prevalence to avoid unnecessary surgery of benign tumors such as myelolipomas. Imaging in the follow-up of the patients with CAH may be considered, especially if the patient has abdominal pain since this is a common presentation of myelolipomas. Moreover, CAH may be considered in every patient with a myelolipoma.

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Legends for Figures and Tables

Figure 1. Flow Diagram of Process of Systematic Review

Table 1. Prevalence of Adrenal Tumors in Patients with Congenital Adrenal Hyperplasia

Table 2. Meta-Analysis of 59 Cases with 21-hydroxylase deficiency and Adrenal Tumors

Table 3. Clinical Characteristics of Myelolipoma in Congenital Adrenal Hyperplasia due to 21-hydroxylase deficiency

Figure 1

Table 1. Prevalence of Adrenal Tumors in Patients with Congenital Adrenal Hyperplasia

First author	Year	Country	Title	Definition of tumor	CAH cases with adrenal tumors of total screened CAH cases	CAH cases with adrenal tumors ≥ 10 mm of total screened CAH cases
El-Maouche D (22)	2019	USA	Adrenal morphology and associated comorbidities in congenital adrenal hyperplasia	≥ 5 mm	19/88 (21.6%)	15/88
Nermoen I (10)	2011	Norge	High frequency of adrenal myelolipoma and testicular adrenal rest tumors in adult Norwegian with classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency	≥ 10 mm	7/62 (11.3%)	7/62 (11.3%)
Reisch N (24)	2010	Germany	Total adrenal volume but not testicular adrenal rest tumor volume is associated with hormonal control in patients with 21-hydroxylase deficiency	≥ 5 mm	15/26 (57.7%)	7/26 (26.9%)
Jaresch S (9)	1992	Germany	Adrenal incidentaloma and patients with homozygous or heterozygous congenital adrenal hyperplasia	≥ 5 mm	18/22 (81.8%)*	9/22 (40.9%)
Azziz R (23)	1991	USA	Magnetic resonance imaging of the adrenal gland in women with late- onset adrenal hyperplasia	≥ 10 mm	1/4 (25.0%)**	1/4 (25.0%)**
Falke TH (21)	1986	The Netherlands	Computed tomography in untreated adults with virilizing congenital adrenal hyperplasia	Only definition of adrenal enlargement:Thickening of limb junction >10 mm	3/13 (23.1%)***	3/13 (23.1%)***
Prevalence of adrenal tumors in CAH (all studies)					63/215 (29.3%)	42/215(19.5%)
Prevalence of adrenal tumors in CAH due to 21OHD (all studies)						
Prevalence of adrenal tumors in CAH due to 21OHD (CAH verified with CYP21A2 mutations)						
Prevalence of myelolipoma in CAH due to 21OHD (all studies)						
Prevalence of myelolipoma in CAH due to 21OHD (CAH verified with CYP21A2 mutations)						
Proportion myelolipom in adrenal tumors in CAH due to 21OHD (CAH verified with CYP21A2 mutations)						
Proportion myelolipom in adrenal tumors in CAH (all studies)						

ND, no data

*Two were diagnosed with 3β -hydroxysteroid dehydrogenase deficiency and 11β -hydroxylase deficiency and both had adrenal tumors**One was diagnosed with 11β -hydroxylase deficiency and had no tumor***Two were diagnosed with 11β -hydroxylase deficiency and both had adrenal tumors

CAH cases due to 21OHD with adrenal tumors	CAH cases due to 21OHD with adrenal tumors ≥ 10 mm	CAH cases with myelolipoma of total screened CAH cases	CAH cases due to 21OHD with myelolipom	CYP21A2 mutations verification	Tumor classification
19/86 (22.1%)	15/86 (17.4%)	11/88 (12.5%)	11/86 (12.8%)	yes	11 myelolipoma 8 adenoma 1 pheochromocytoma
7/62 (11.3%)	7/62 (11.3%)	4/62 (6.5%)	4/62 (6.5%)	yes	4 myelolipoma 2 adenoma 1 pheochromocytoma
15/26 (57.7%)	7/26 (26.9%)	0/26 (0%)	0/26 (0%)	yes	ND
16/20 (80.0%)	7/20 (35.0%)	1/22 (4.5%)	1/20 (5.0%)	no	ND, but 3 large tumors were operated because they were >6 cm (1 myelolipoma, 1 adenoma and 1 nodular hyperplasia)
1/3 (33.3%)	1/3 (33.3%)	0/4 (0%)	0/3 (0%)	no	1 adenoma
1/11 (9.1%)	1/11 (9.1%)	0/13 (0%)	0/11 (0%)	no	2 adenoma 1 not classified
59/208 (28.4%) 41/174 (23.6%)	38/208 (18.3%) 29/174 (16.7%)		16/208 (7.7%) 15/174 (8.6%) 15/41 (36.6%)		
		16/63 (25.4%)			

Table 2. Meta-Analysis of 59 Cases with 21-hydroxylase deficiency and Adrenal Tumors

First author and ratio of patients with tumor (ref)	Imaging modality	Age at tumor diagnoses (years) (median and range)	Gender N (%)
El-Maouche D 19/88 (22)***	CT	38.0 (16-65)	12 in 41 male (29.3%) 7 in 47 female (14.9%)
Nermoen I, 7/62 (10)***	CT with contrast	38.0 (27-58)	5 in 23 male (21.7%) 2 in 39 female (5.1%)
Reisch N, 15/26 (24)	MR	ND [age of total study population 33.0 years (18-48)]	15 in 25 male (60.0%) (no female in study)
Jaresch S, 16/20 (9)	CT with contrast	25.0 (12-60)	13 in 15 female (86.7%) 3 in 5 male (60.0%)
Azziz R, 1/3 (23)	MR	34.0	1 in 3 female (33.3%) (no male in study)
Falke TH, 1/11 (21)	CT with contrast	48.0	1 46,XX male with tumor (gender not stated in 6 cases)
Results		36.0 (12-60)*	36/95 male (37.9%)** 23/104 female (22.1%)** P<0.05

*Reisch not included. **Falke not included. ***Some data obtained after contact with the corresponding author. CT, computed tomography, MRI, magnetic resonance imaging, ND, no data, SW, salt wasting. SV, simple virilization.

Size of adrenal tumor (mm) (median and range)	Bilateral N (%)	Adrenal side N (%)	Subtype of 21-OHD* N (%)
15.0 (5-100)	7 (38%)	9 (47.4%) left	13 (68.4%)SW
		3 (15.8%) right	6 (31.6%)SV
35.0 (12-165)	2 (28.6%)	3 (42.9%) left	5 (71.4%)SW
		2 (28.6%) right	2 (28.6%) SV
10.0 (6-37)	ND	ND	ND
5-9 (5->50)	1 (6.3%)	12 (75.0%) left	11 (68.8%) SV
		3 (18.8%) right	5 (31.3%)NC
33.0	0 (0%)	1 (100%) left	1 (100%)NC
55.0	0 (0%)	1 (100%) right	1 (100%) SV
24.0 (5-165)	10/44 (22.7%)*	left 25/44 (56.8%)*	SW 18/44 (40.9%)
		right 9/44 (20.1%)*	SV 20/44 (45.5%)
		P<0.05	NC 6/44 (13.6%)

author
rilizing, NC, nonclassic

First author (ref)	Year	Country	Title	CAH form	Symptoms when diagnosed myeloidipoma	Age when myeloidipoma diagnosed (years)	Age when CAH diagnosed (years)	Poorly managed or diagnosed CAH late	Gender	Tumor size (mm)	Tumor side*	Bilateral
Schneider H (25)	1975	Austria	Myeloidipoma of the adrenal gland in adrenogenital syndrome	21OHD, SV	Virilization	54	53	yes	female	137	left	no
Boudreaux D (26)	1979	USA	Giant adrenal myeloidipoma and testicular interstitial cell tumor in a man with congenital 21-hydroxylase deficiency	21OHD, SW	Dyspnea, low thoracic pain	57	57	yes	male	340	left	no
Oliva A (27)	1988	USA	Myeloidipoma and endocrine dysfunction	21OHD, SV	Left flank pain and hypotension	34	62	yes	female	130	left	no
Miyazaki Y (28)	1990	Japan	A case of adrenal myeloidipoma associated with adrenogenital syndrome	21OHD, SV	Abdominal discomfort	50	50	yes	female	50	left	no
Murakami C (29)	1992	Japan	Adrenal myeloidipoma associated with congenital adrenal 21-hydroxylase deficiency	21OHD, SV	Asymptomatic, abnormal liver function	41	41	yes	male	30	yes	no
Iwamoto T (30)	1993	Japan	Reversible male infertility due to CAH	21OHD, SV	Infertility	32	32	yes	male	50	yes	yes
Ravichandran R (31)	1996	USA	CAH presenting as massive adrenal incidentalomas in the sixth decade of life: Report of two patients with 21-hydroxylase deficiency	21OHD, SV	Asymptomatic	58	58	yes	male (46,XX)	100	right	no
Umpierrez M (32)	1997	USA	Adrenal myeloidipoma associated with endocrine dysfunction: review of the literature	21OHD, SV	Chronic back pain	47	47	yes	male	35	yes	no
Adeskan A (33)	1997	USA	Testicular "tumor" of the adrenogenital syndrome: a case report of an unusual association with myeloidipoma and seminoma in cryptorchidism	21OHD, SV	Left inguinal pain	44	44	yes	male	20	left	no
Allison KH (34)	2003	USA	An unusual case of multiple giant myeloidipomas: clinical and pathogenetic implications	21OHD, SV	Increased abdominal girth and weight loss	43	43	yes	male	430	left	no
Mathew J (35)	2005	India	An elderly lady in shock	21OHD, SV	Extreme exhaustion and breathlessness	62	62	yes	female	120	yes	yes
Kalidindi RS (36)	2006	UK	Bilateral giant adrenal myeloidipomas	21OHD, SV	Asymptomatic, detected by palpation	42	42	yes	male	250	yes	yes
Treska V (37)	2006	Czech rep.	Giant bilateral adrenal myeloidipoma associated with CAH	21OHD, SV	Virilization and abdominal discomfort	56	56	yes	female	160	yes	yes
Sakaki M (38)	2006	Japan	Bilateral adrenal myeloidipoma associated with adrenogenital syndrome	21OHD, SV	Fever, nausea and vomiting	69	69	yes	female	80	yes	yes
Rodriguez-Vallejo F (39)	2006	Mexico	Two Siblings With Untreated CYP21 Deficiency and Giant Myeloidipomas: Case Report and Review of the Literature	21OHD, SV	Dull pain in the left upper abdomen	31	<1	yes	female	300	left	no
Rodriguez-Vallejo F (39)	2006	Mexico	" " " "	21OHD, SV	Asymptomatic	29	<1	yes	female	280	yes	yes
Rajput R (40)	2007	India	Evolution of adrenal myeloidipoma in a patient with CAH	21OHD, SV	Asymptomatic	27	20	yes	female	nd	left	no
Nigawara Y (41)	2008	Japan	A Male Case of Nonclassical 21-hydroxylase Deficiency First Manifested in His Sixties with Adrenocortical Incidentaloma	21OHD, SV/NC	Asymptomatic	66	66	yes	male	60	right	no
Hagihara H (42)	2008	Japan	Lack of ACTH and androgen receptor expression in a giant adrenal myeloidipoma associated with 21-hydroxylase deficiency.	21OHD, SV	Asymptomatic	43	6	yes	female	170	left	no
Nermoen I* (43)	2009	Norway	Two adults with adrenal myeloidipoma and 21-hydroxylase deficiency	21OHD, SV	Fatigue, nausea and impotence	68	68	yes	male	40	right	no
Mara Memejo L (44)	2010	Brazil	Giant adrenal myeloidipoma associated with 21-hydroxylase deficiency: unusual association mimicking an androgen-secreting adrenocortical carcinoma	21OHD, SV	Abdominal pain	57	57	yes	male	150	left	no
Ioannidis O (45)	2011	Greece	Giant bilateral symptomatic adrenal myeloidipomas associated with CAH	21OHD, SV	Diffuse abdominal pain and vomiting	34	<1	yes	female	240	yes	yes
German-Mena E (46)	2011	USA	Adrenal myeloidipomas in patients with CAH: review of the literature and a case report	21OHD, SV	Increasing abdominal girth and pain	45	45	yes	male	244	yes	yes
Nermoen I* (10)	2011	Norway	High frequency of adrenal myeloidipomas and testicular adrenal rest tumours in adult Norwegian patients with classical	21OHD, SV	Asymptomatic	38	<1	yes	male	35	yes	yes
Nermoen I (10)	2011	Norway	CAH because of 21-hydroxylase deficiency	21OHD, SW	Asymptomatic	38	<1	no	male	33	left	no
Nermoen I (10)	2011	Norway	" " " "	21OHD, SW	Asymptomatic	40	<1	yes	male	40	left	no
Nermoen I (10)	2011	Norway	" " " "	21OHD, SV	Asymptomatic	50	9	yes	male	57	right	no
McGeoh SC (47)	2012	UK	Giant bilateral myeloidipomas in a man with CAH	21OHD, SW	Abdominal swelling and discomfort	34	<1	yes	male	230	yes	yes
Garduño-García J de J (48)	2013	Mexico	Late-occurring giant adrenal myeloidipoma in a patient with CAH	21OHD, SV	Abdominal pain and bloating over the past year	64	<1	yes	female	210	yes	yes
Ferreira F (49)	2013	Portugal	Rare and severe complications of CAH due to 21-hydroxylase deficiency: a case report	21OHD, SW	Addison crisis	35	<2	yes	male	120	yes	yes
Sancak S (50)	2013	Turkey	Bilateral adrenal myeloidipoma in a 46 XX DSD patient with CAH due to 21-hydroxylase deficiency: Case report	21OHD, SV	Diffuse abdominal pain	35	35	yes	male (46,XX)	91	yes	yes
Almeida MQ (51)	2014	Brazil	Increased expression of ACTH (MCR2) and androgen (AR) receptors in giant bilateral myeloidipomas from patients with CAH	21OHD, SV	Asymptomatic	35	20	yes	female	140	yes	yes
Almeida MQ (51)	2014	Brazil	" " " "	21OHD, SV	Asymptomatic	52	52	yes	female	160	yes	yes
Alvarez JF (52)	2014	USA	Giant adrenal myeloidipoma	21OHD, SV	Progressive abdominal distention, nausea, emesis	44	<1	yes	female	340	left	no
Al-Bahri S (53)	2014	USA	Giant Bilateral Adrenal Myeloidipoma with CAH	21OHD, SV	Fatigue, decreased libido, increased abdominal distension	39	<1	yes	male	300	yes	yes
Kale G (54)	2015	USA	Giant myeloidipomas and inadvertent bilateral adrenalectomy in classic CAH	21OHD, SW	Chronic back pain, lower extremity paresthesia	51		yes	male	311	yes	yes
O'Shea T (55)	2016	Ireland	Growth of a progesterone receptor-positive meningioma in a female patient with CAH	21OHD, SV	Frontal headache and marked right-sided ptosis	45	<7	yes	female	450	yes	yes
Okamoto S (56)	2016	Japan	An adult case of CAH due to 21-hydroxylase deficiency associated with bilateral adrenal myeloidipoma: An 8-year observation of clinical characteristics during steroid replacement therapy	21OHD, SV	Flank pain	44	44	yes	male	140	yes	yes
Altieri VM (57)	2016	Italy	Leydig cell tumour and giant adrenal myeloidipoma associated with adrenogenital syndrome: a case report with review of the literature	21OHD, SV	Abdominal pain	27	4	no	male	140	yes	yes
Feng X (58)	2017	Canada	Massive adrenal incidentaloma and late diagnosis of CAH in prostate cancer	21OHD, SV	Asymptomatic	61	61	yes	male	180	yes	yes
Liu Q (59)	2018	China	Giant bilateral adrenal myeloidipomas in two Chinese families with CAH and adrenal myeloidipoma	21OHD, SV	Abdominal pain	59	59	yes	male	260*	yes	yes
Liu Q (59)	2018	China	" " " "	21OHD, SV	ND	50	60	yes	male	ND	yes	yes
Kim HJ (60)	2019	Korea	Adrenal myeloidipoma in association with CAH	21OHD, SV	Gastroesophageal reflux	64	72	yes	male	125	left	no
Sucharitkittkongs S (61)	2019	USA	Bilateral adrenal myeloidipomas presenting as acute adrenal insufficiency in an adult with CAH	21OHD, SV	Acute adrenal insufficiency	39	39	yes	male (46,XX)	60	yes	yes
Piskapas HP (62)	2019	Turkey	Bilateral Adrenal and Testicular Mass in a Patient with CAH	21OHD, SV	Asymptomatic, but bilateral testicular masses	41	41	yes	male	88	yes	yes
Pakakis MG (63)	2019	USA	Adrenal collision tumour comprised of adrenocortical carcinoma and myeloidipoma in a patient with CAH	21OHD, SV	Pressor-dependent shock	61	ND	yes	male	103	yes	yes
El-Masche D** (22)	2019	USA	Adrenal morphology and associated comorbidities in CAH	21OHD, SW	Asymptomatic	53	ND	ND	male	100	yes	yes
" " " "	" " " "	" " " "	" " " "	21OHD, SV	Asymptomatic	29	ND	ND	female	79	left	no
" " " "	" " " "	" " " "	" " " "	21OHD, SV	Asymptomatic	42	ND	ND	male	65	yes	yes
" " " "	" " " "	" " " "	" " " "	21OHD, SV	Asymptomatic	40	ND	ND	female	25	yes	yes
" " " "	" " " "	" " " "	" " " "	21OHD, SW	Asymptomatic	38	ND	ND	female	36	yes	yes
" " " "	" " " "	" " " "	" " " "	21OHD, SW	Asymptomatic	19	ND	ND	male	15	left	no
" " " "	" " " "	" " " "	" " " "	21OHD, SW	Asymptomatic	56	ND	ND	male	39	yes	yes
" " " "	" " " "	" " " "	" " " "	21OHD, SW	Asymptomatic	31	ND	ND	male	28	right	no
" " " "	" " " "	" " " "	" " " "	21OHD, SW	Asymptomatic	48	ND	ND	male	5	yes	yes
" " " "	" " " "	" " " "	" " " "	21OHD, SW	Asymptomatic	52	ND	ND	male	25	left	no
" " " "	" " " "	" " " "	" " " "	21OHD, SV	Asymptomatic	65	ND	ND	male	13	left	no
Results for the 57 patients with 21OHD and myeloidipoma				14 (24.6%)SV	26 (45.6%) asymptomatic	44 (19-69)	41 (1-72)	44 of 46 (95.7%)	38 (66.7%)	102.1 (4-430)	left 18 (31.6%)	34 (59.6%)
				41 (75.4%)SV	19 (33.3%) abdominal or flank/thoracic pain	median (range)	median (range)		male	median (range)	right 5 (8.2%)	
				19 (33.3%) female								

ND=no data, * Nermoen published data in one patients twice and we included the patient once, **The corresponding author were contacted for some missing data