Clinical features and aetiology of newly diagnosed adrenal insufficiency: A single-centre retrospective cross-sectional study in Japan.

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Abstract

Background: Central adrenal insufficiency (AI) has been reported to be twice as common as primary AI outside Japan. The most common causes of central AI are drugs and pituitary tumours. However, given the significant differences in the incidence rates of Addison's disease and isolated ACTH deficiency between Japan and other countries, the most common causes of AI in Japan may differ from those in other countries. Furthermore, few studies have focused on the clinical features of newly diagnosed central AI.

Methods: A retrospective single-centre observational study using electronic medical records from April 2012 to December 2019 was conducted. The main outcome was the proportion of cases of central AI among all cases of newly diagnosed AI. We also investigated the clinical features and common causes of central AI. Only patients with AI confirmed with hormone tests were included. Patients with AI who were asymptomatic or diagnosed clinically without hormone test confirmation were excluded. Based on hormone tests and the clinical diagnosis, AI was classified into primary and central AI.

Results: A total of 34 patients were eligible. The mean patient age was 76.3 years, 11 (32.4%) were women, and 11 (32.4%) were former or current users of glucocorticoids for non-endocrine diseases. Of the 34 patients with newly diagnosed AI, all (100.0%) had central AI. The most common cause of central AI was glucocorticoids (n = 11, 32.4%), followed by central hypoadrenalism of unknown causes (n = 9, 26.5%), idiopathic isolated ACTH deficiency (n = 6, 17.7%), and pituitary tumours (n = 5, 14.7%). For the 34 patients with central AI, the mean time to receive a correct diagnosis from the onset was 6.2 months. The most common symptoms at diagnosis were anorexia (n = 26, 76.5%), fatigue (n = 23, 67.6%), asthenia (n = 22, 64.7%) and nausea or vomiting (n = 19, 55.9%).

Conclusions: Primary AI is rare in Japan. The most common cause of newly diagnosed central AI is glucocorticoid use. Pituitary tumours may be a less common cause of central AI in Japan than in other countries.

Background

Adrenal insufficiency (AI) is a life-threatening disorderthatresults from adrenal failure due to impairment ofthehypothalamic-pituitary-adrenal axis [1]. AI is uncommon, butadelay in its diagnosis leads to a fatal event. Nonetheless,delaysin the diagnosis of AI are common [2,3]. To preventdiagnosticdelay, it is important to know the common causes andpresentingfeatures of AI.

AI is classified as primary and central (including secondaryandtertiary) based on the underlying mechanism [1]. Recent andpastreviews reported that the prevalence and incidence of centralAIare estimated to be approximately twice as frequent as thoseofprimary AI [4], and the most common causes of central Alareglucocorticoids and pituitary tumours [1,4-7]. However, most ofthepast studies cited in those reviews investigated theepidemiologyof primary AI [2,8-14] and central AI [10,15-18]separately.Moreover, all past studies investigating theepidemiology ofcentral AI targeted patients with

hypopituitarism[15,17,18] orpituitary adenoma [16] rather than patients withhypoadrenalism. Inaddition, glucocorticoid-induced AI, which isconsidered to be themost common type of central AI [1,4-7,19-21],was not included inthose studies [2,8-18]. Thus, no studies havefocused on theaetiology of newly diagnosed AI includingglucocorticoid-induced AI[4]. Furthermore, given that past studiessuggested that there aresubstantial differences in the prevalencerates of Addison'sdisease [11,13,22,23] and idiopathic isolatedadrenocorticotropichormone (ACTH) deficiency [24,25] between Japanand othercountries, it is possible that the frequency of causes ofAI inJapan is different from that in other countries. Inclinicalpractice, when AI is diagnosed, whether AI is caused bydiseases ofthe adrenal gland (primary) or pituitary gland orhypothalamus(central) is subsequently investigated [1,26,27].Therefore,knowing the frequency of causes of newly diagnosed Alisimportant.

With regard to the clinical features of AI, most ofthereferences cited in the reviews [1,7,19] andendocrinologytextbooks [20] are old studies published more than twodecades ago[28-31]. Furthermore, few studies have focused on thefeatures ofcentral AI at presentation [4,29] because most paststudiesinvestigated only clinical features of central AI due tospecificaetiologies [24,30,32-35], such as pituitary apoplexy[34,35] oridiopathic isolated ACTH deficiency [24,30,32]. Inaddition, nostudies have been conducted to investigate the clinicalfeatures ofglucocorticoid-induced AI because nearly all studiesregardingglucocorticoid-induced AI targeted asymptomatic ratherthansymptomatic biochemical AI induced by glucocorticoiduse[21,36-39]. Therefore, more studies are needed to investigatethefeatures at presentation, particularly for central AI.

Thus, the aim of our study was to determine the frequencyofcauses of newly diagnosed AI and investigate the featuresofcentral AI at presentation. We investigated the proportion ofcasesof central AI among all newly diagnosed AI cases andevaluatedwhether glucocorticoid use for non-endocrine diseases andpituitarytumours are the most common causes of central AI inJapan.

Methods

Study setting and design

To investigate the aetiology of newly diagnosed AI, weconducteda retrospective single-centre cross-sectional study usingmedicalelectronic records. Our hospital is a 350-bed communitygeneralhospital, and it is one of the two largest hospitals,coveringapproximately 0.5 million people in Utsunomiya,Japan.

Inclusion and exclusion criteria

Patients who were 18 years old or older and who werenewlydiagnosed with AI and started hormone replacement therapyduringthe study period were included. We included only patients whometall the following criteria: (1) the presence of somesymptomsconsistent with AI; (2) hormone test confirmation of AI;and (3)started glucocorticoid replacement therapy. Patients with Althatwas diagnosed at another hospital during the study periodwereexcluded.

Definitions

Based on past reviews [1,40,41] and guidelines [42], apatientswas considered to have AI that was confirmed by a hormonetest ifany of the following criteria were satisfied: (1) a serumcortisollevel less than 5 μg per decilitre in the morning (from8:00 A.M.to 9:00 A.M.) or (2) a serum cortisol level from 5 to 18μg perdecilitre in the morning and a peak serum cortisol level lessthan18 μg per decilitre at 30 minutes and 60 minutes during the250-μgcorticotropin stimulation test or insulin-inducedhypoglycaemiatest. Central AI was differentiated from primary AI bymeans of themorning plasma ACTH level. Based on past studies andreviews[26,42,43], primary AI was defined as AI with a plasma ACTHlevelgreater than 2 times the upper limit of the referencerange.Otherwise, AI was classified as central AI. There is noconsensusfor the definition of idiopathic isolated ACTH deficiency.Based onpast cases and reviews [24,32,44,45], idiopathic isolatedACTHdeficiency was identified if the following criteria were allmet:(1) central AI was confirmed by hormone tests; (2) no signsorlaboratory findings suggested deficiencies in otheranteriorpituitary hormones; and (3) no organic pituitary lesionwasobserved on brain imaging.

Screening anddatacollection

We identified patients with AI from the database of ourhospital.All patients who were diagnosed with AI in outpatient andinpatientsettings from April 2012 to December 2019 were identifiedusing theInternational Statistical Classification of Diseases andRelatedHealth Problems codes (more detailed information is shownin thesupplementary file; Table S1). An initial search identified131patients during the study period. Of those, 47 patients werenewlydiagnosed with AI and treated by hormone replacement.Afterexcluding 12 patients who were treated by hormonereplacementwithout confirmation by hormone tests, a total of 34patients wereincluded in the final analysis (Figure).

Physicians (JK, MM) independently reviewed the electronicmedicalrecords and retrieved information on patient age, sex, pastmedicalhistory, medication use, vital signs, time to a correctdiagnosisfrom symptom onset, symptoms, physical findings,laboratoryfindings, imaging results, aetiology of AI, treatmentfor AI, andprognosis. Discrepancies between the two investigatorswere resolvedby discussion. The last follow-up date forinformation on prognosiswas 17 December 2019.

Outcome measures

The primary outcome was the proportion of patients whowerediagnosed with central AI among all patients newly diagnosedwithAI. The secondary outcomes were the proportions of patientswhowere diagnosed with glucocorticoid-induced AI and AI duetopituitary tumours among those newly diagnosed with central AI.Wealso investigated the frequency of presenting symptoms andclinicalfindings of central AI stratified by whether the AI was duetoglucocorticoids or other causes.

Statistical analysis

The baseline characteristics of the study populationarepresented as descriptive statistics. The comparisons ofclinicalfeatures between patients who were diagnosedwithglucocorticoid-induced AI and

central AI due to other causeswereperformed by using Fisher's exact test for categoricalvariablesand Student's t-test for continuous variables. Based ontheanecdotal evidence that most physicians candiagnoseglucocorticoid-induced AI with few tests needed [46], wetested thehypothesis of whether the time to correct diagnosis fromonset isfaster for glucocorticoid-induced AI than for central AIdue toother causes. The level of statistical significance was setat 5%.Stata version 15 (LightStone, Tokyo, Japan) or Excelstatisticalsoftware package version 2.11 (Bellcurve for Excel;Social SurveyResearch Information Co., Ltd., Tokyo, Japan) wereused for theseanalyses.

Results

The baseline characteristics of the 34 patients who werenewlydiagnosed with AI are shown in Table 1 (detailed informationisshown in the supplementary file; Table S2). The mean age was76.3years old (SD 14.1), 11 (32.4%) were women, and 11 (32.4%)werecurrent or former glucocorticoid users for non-endocrinediseases.With regard to their past medical history, 7 (20.6%) hadarheumatological disease, 1 (2.9%) had a pituitary tumour, and1(2.9%) had autoimmune thyroid disease. No patients had apasthistory of Cushing's disease, acromegaly, or type 1diabetesmellitus. The mean morning serum cortisol and plasmaACTHconcentrations were 4.1 micrograms per decilitre (SD 3.4) and15.0picograms per millilitre (SD 10.7), respectively (moredetailedinformation is shown in the supplementary file; Table S3).Of the34 patients, all (100%) were classified as having central AI,andthere were no patients who were classified as having primaryAIduring the study period. The most common cause of central AIwasglucocorticoid use (n = 11, 32.4%), followed by unspecifiedorunknown cause (n = 9, 26.5%), idiopathic isolated ACTHdeficiency(n = 6, 17.7%), and pituitary tumour (n = 5, 14.7%). Ofthe 5patients with pituitary tumours, 4 had non-functioningpituitaryadenomas, and one had a Rathke's cleft cyst.

Among the 34 patients with central AI, the mean time to acorrectdiagnosis from onset was 6.2 months (SD 10.2). In total, 15(44.1%)and 28 (82.4%) were diagnosed correctly within one monthand oneyear from onset, respectively. The time to a correctdiagnosis fromonset for central AI due to other causes wassignificantly longerthan that for glucocorticoid-induced AI(p = 0.03) (Table2). The most common symptom of centralAI at diagnosis was anorexia(n = 26, 76.5%), followed by fatigueor malaise (n = 23, 67.6%),asthenia (n = 22, 64.7%) and nausea orvomiting (n = 19, 55.9%).Although fatigue or malaise (p =0.001) and asthenia(p = 0.01) were significantly morecommonly seen inpatients with glucocorticoid-induced AI than inpatients withcentral AI due to other causes, there were nosignificantdifferences in other symptoms between the two groups.Regarding thelaboratory findings of the 34 patients with centralAI, the meanserum concentrations of sodium, potassium, and glucosewere 134milliequivalents per litre (SD 12), 4.3 milliequivalentsper litre(SD 0.8), and 110 milligrams per decilitre (SD 62),respectively.While the serum concentration of potassium wassignificantly lowerin patients with glucocorticoid-induced AIsthan those with centralAI due to other causes (p = 0.04),the serum concentrationof glucose was higher in patients withglucocorticoid-induced AIsthan those with central AI due to othercauses (p = 0.003).Compared with patients withglucocorticoid-induced AI, patients withcentral AI due to othercauses more often had hyponatremia due tosyndrome of inappropriatesecretion of antidiuretic hormone (SIADH)(0% versus 39.1%,p = 0.02).

Of the 34 patients with central AI, 34 (100.0%), 4 (11.8%), and1(2.9%) initiated treatment with hormone replacementforglucocorticoids, thyroid hormone, and desmopressin,respectively,after diagnosis. During the mean follow-up time of12.9 months, onecardiovascular event (2.9%) and five deaths (14.7%)occurred.

Discussion

Our findings show that the frequency of central AI is muchhigherthan that of primary AI in a Japanese hospital. Given thatprimaryAI and central AI occur in a 1:2 ratio based on paststudiesconducted outside Japan [4], it is surprising that no casesofprimary AI were diagnosed while more than 20 cases of centralAIwere diagnosed during the same period in this study.Nonetheless,this result may be supported by past studies reportingthatAddison's disease is much less common in Japan than inothercountries [11,13,22,23].

In the present study, the most common cause of newlydiagnosedcentral AI was glucocorticoids. This result supportsindirectevidence [1,4-7,19-21,36-39] that the most common cause ofcentralAI is probably glucocorticoids because the prevalence ratesofchronic glucocorticoid use and biochemical AI amongglucocorticoidusers are high [21,36-39]. However, AI due topituitary tumoursaccounted for less than one-fourth of all cases ofnewly diagnosedcentral AI excluding glucocorticoid-induced AI inthis study. Thisresult is not consistent with the results of paststudies thatreported that more than two-thirds of central Alexcludingglucocorticoid-induced AI was caused by pituitarytumours[3,7,15,17,18]. Given that these past studies [3,15,17,18]wereconducted outside Japan and idiopathic isolated ACTH deficiencymaybe more common in Japan than in other countries [24,25],ourfinding suggests that pituitary tumours are a relativelylesscommon cause of central AI in Japan. However, our studyhaslimitations due to the small sample size and single-centrestudydesign. Furthermore, given that few studies have focused ontheaetiology of newly diagnosed central AI and most paststudiestargeted hypopituitarism rather than hypoadrenalism[15,17,18],further studies are needed to investigate the aetiologyof newlydiagnosed central AI in Japan and other countries.

In the present study, approximately 20% of all newly diagnosedAIwas diagnosed more than one year after onset. Our findingisconsistent with that of past studies showing that diagnosticdelayof AI is common [2,3]. Moreover, the time to correct diagnosisfromthe onset was significantly shorter for patientswithglucocorticoid-induced AI than for those with central AI duetoother causes in this study. This result supports anecdotalevidence[41,46] that glucocorticoid-induced AI is easier todiagnose thancentral AI due to other causes. To improve thisdiagnostic delay,further studies investigating associated factorsare warranted.

With regard to the features of central AI atpresentation,excluding glucocorticoid-induced AI, our findings areconsistentwith those of past studies [3,29], showing that the mostcommonsymptoms are fatigue, asthenia, and gastrointestinalsymptoms; itis noteworthy that one [3] of the two previous studieshad recallbias because the survey was administered a long timeafter thediagnosis was made. However, abdominal pain and diarrhoeaasgastrointestinal symptoms were relatively less common inthisstudy,

although other gastrointestinal symptoms were common.Thiswas also consistent with the findings of past studies thatshowedthat abdominal pain and diarrhoea were less common inpatients withcentral AI than in those with primary AI [3,29]. Inthe presentstudy, a substantial proportion of patients with centralAI hadhypoglycaemic episodes and hyponatremia before diagnosis.Theseresults are also consistent with the results of paststudiesinvestigating the clinical features of isolated ACTHdeficiency[24,30,32] or central AI [29].

To the best of our knowledge, this study was the firsttoinvestigate the features of glucocorticoid-induced AI at thetimeof presentation because past studies on glucocorticoid-inducedAItargeted asymptomatic rather than asymptomatic AI inglucocorticoidusers [21,36-39]. There was no difference in clinicalfeaturesbetween glucocorticoid-induced AI and central AI due toothercauses. However, fatigue and asthenia were less common inpatientswith glucocorticoid-induced AI than those with central AIdue toother causes. Moreover, hypoglycaemic episodes andhyponatremiawere also less frequent in patients withglucocorticoid-induced AIthan in those with central AI due to othercauses. Given that thetime to correct diagnosis was shorter inpatients withglucocorticoid-induced AI than in those with centralAI of othercauses, these symptoms and findings may develop if AI isnottreated promptly after onset.

Strengths and weaknesses

To the best of our knowledge, this was the first studytodetermine the aetiology of newly diagnosed AI and investigatetheclinical features of central AI, includingglucocorticoid-inducedAI. To avoid including diseases other thanAI, we included onlycases of AI that were confirmed by hormonetests. Moreover, becausenone of the hormone tests, including theinsulin tolerance test,correctly classifies all patients with AI[1,7,40], only patientswho were symptomatic and treated by hormonereplacement wereincluded.

However, our findings should be interpreted cautiously.First,our study was a retrospective observational study. Therefore,thedata extracted for use in this study might not beaccurate.Moreover, AI that was not coded by the attendingphysicians wasmissed in this study. Second, we excluded AI that wasdiagnosedclinically without confirmation by hormone tests. However,none ofthe 13 excluded patients who had AI treated by hormonereplacementtherapy without confirmation by hormone tests hadprimary AI.Furthermore, even if the 5 excluded patients with AI whoweretreated by hormone replacement therapy after surgery forpituitarytumours who lacked AI symptoms and confirmation fromhormone testswere included in this study, AI due to pituitarytumours accountedfor less than half of the cases of central AI.Third, our study wasa single-centre study with a small sample size.Therefore, furthermulticentre studies should be performed toinvestigate theaetiology of newly diagnosed AI. Fourth, the use ofunprescribedcorticosteroid-like agents [41] is not routinelyassessed in ourhospital. Moreover, the assessment of the effect oftopical andintra-articular glucocorticoid use on AI might beinsufficient.Therefore, the frequency of drug-induced AI mightbeunderestimated. Fifth, given the limited sensitivity of the250-μgcorticotropin stimulation test for central AI, particularlyin theearly phase after onset [47,48], the frequency of central AImighthave been underestimated. Sixth, pituitary hormones otherthancorticotropin were not routinely investigated by laboratorytestswithout clinical suspicion of

deficiency. Therefore,deficienciesof other pituitary hormones, which could affect thesymptoms andsigns of patients, might have beenunderestimated.

Implications for clinical practice

In the present study, primary AI was rare and pituitarytumoursaccount for less than one-fourth of the cases of central AI.In areview article published 80 years ago, Sheehan stated that thetruetype of central AI due to tumours is rare [33]. Ourfindingssuggest that pituitary tumours may not be common causes ofcentralAI in Japan, unlike in other countries. However, given thatfewstudies have focused on the aetiology of newly diagnosed centralAI[4] and that most past studies conducted in countries outsideofJapan [15-18] targeted hypopituitarism and nothypoadrenalism,further studies are warranted to investigate theaetiology of newlydiagnosed central AI in Japan and othercountries.

Conclusions

Primary AI is rare in Japan. The most common cause ofnewlydiagnosed central AI is glucocorticoid use, and the proportionofpatients with AI caused by pituitary tumours may be smallerinJapan than in other countries. The most common symptoms ofcentralAI are fatigue, asthenia, and gastrointestinal symptoms,andhypoglycaemic episodes and hyponatremia are sometimesconcomitant.Further studies investigating the aetiology of newlydiagnosed AIand evaluating the clinical features of central AI areneeded.

Abbreviations

AI: adrenal insufficiency; ACTH: adrenocorticotropic hormone;SD:standard deviation; SIADH: syndrome of inappropriate secretionofantidiuretic hormone.

Declarations

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Availability of data and materials

All data generated or analysed during this study are includedinthis manuscript and the additional file.

Authors' contributors

JK and MM conceived of and designed this study. JK wrotetheprotocol for this study. JK and MM collected the data. JKanalysedand guarantee the data. JK wrote the draft of themanuscript. Allauthors contributed to the revision of themanuscript and read andapproved the final manuscript.

Ethics approval and consent to participate

The protocol of this research was approved by the MedicalEthicalCommittee of the National Hospital Organization TochigiMedicalCentre (No. 2019-15). We conducted the research inaccordance withthe Ethical Guidelines for Epidemiological Researchin Japan and theDeclaration of Helsinki. The need for individualinformed consentwas formally waived by the Medical EthicsCommittee of the NationalHospital Organization Tochigi MedicalCentre because we collecteddeidentified data without contactingthe patients. However, per theJapanese Ethical Guidelines, wedisplayed an opt-out statement inthe waiting room and webpage ofthe hospital to inform patientsabout the study and provide theopportunity for patients to refuseto allow the use of theirdata.

Consent for publication

Not applicable.

Competing interests

None of the authors have financial relationships withanyorganizations that might have an interest in this submitted workorother relationships or activities that could appear tohaveinfluenced the submitted work.

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Tables

Table1. Baseline characteristics of the 34patients who were newly diagnosed with adrenalinsufficiency[a].

Characteristics	Total (n =34)
Mean ageat diagnosis, year (SD)	76.3(14.1)
Femalesex	11(32.4)
Pastmedical history	
Pituitary tumour	1(2.9)
Head trauma	4(11.8)
Autoimmune thyroid disease	1(2.9)
Rheumatological disease	7(20.6)
Major depressive disorder	1(2.9)
Mean timeto diagnosis from onset, months (SD)	6.2(10.3)
Current orformer use of glucocorticoids for non-endocrinedisease	11(32.4)
Pigmentation	1(2.9)
Laboratoryfindings at diagnosis	
White blood cell count (SD)	7200(2800)
Eosinophil cell count (SD)	313(352)
Serumsodium, mEq/dl (SD)	134(12)
Serum potassium, mEq/dl (SD)	4.3(0.8)
Serum glucose, mg/dl (SD)	110(62)
Hyponatremia due to SIADH atdiagnosis	9(26.5)
Morningserum cortisol, µg/dl (SD)	4.1(3.4)
Morningplasma ACTH, pg/ml (SD)	15.0(10.7)
Standarddose short synacthen test	
Serum cortisol at baseline, µg/dl(SD)	5.1(4.3)
Serum cortisol at 30 min, µg/dl (SD)	9.9(4.4)
Serum cortisol at 60 min, µg/dl (SD)	11.2(4.7)
Culpritlesion causing adrenal insufficiency	
Primary adrenal insufficiency	0(0.0)
Central adrenalinsufficiency	
Pituitary	13(38.2)
Hypothalamic	16(47.1)
Unspecified	5(14.7)
Aetiologyof adrenal insufficiency	
Glucocorticoids	11(32.4)
Unspecified or unknown cause	9(26.5)
Isolated ACTH deficiency	6(17.7)
Pituitary tumour or cyst	5(14.7)
Meningoencephalitis	1(2.9)
Giant cerebral aneurysm	1(2.9)
IgG4-associated disease	1(2.9)

[a]Values are expressed as thenumber with the percentage of the total number, unless otherwisestated.
ACTH: adrenocorticotropichormone; SD: standard deviation; SIADH: syndrome ofinappropriate secretion of antidiuretic hormone.

Table2. Comparison of clinicalfeatures between glucocorticoid-induced adrenal insufficiency andcentral adrenal insufficiency due to othercauses[a].

cs	Drug-induced AI (n =11)	Central AI(excluding drug-induced AI) (n =23)	*P*-value[b]
liagnosis, year (SD)	75.7(11.5)	76.6(15.4)	0.87
	4(36.4)	7(30.4)	1.00
·ect diagnosis from onset			
ıs (SD)	0.9(1.0)	8.8(11.7)	0.03
nonth	8(72.7)	7(30.4)	0.03
·ear	11(100.0)	17(73.9)	0.15
of consultations until	2.2(1.1)	3.6(2.3)	0.06
)			
diagnosis			
	8(72.7)	18(78.3)	1.00
ıalaise	3(27.3)	20(87.0)	0.001
	3(27.3)	19(82.6)	0.01
omiting	7(63.6)	12(52.2)	0.71
tal status	3(27.3)	6(26.1)	1.00
	4(36.4)	4(17.4)	0.39
	3(27.3)	5(21.7)	1.00
	2(18.2)	5(21.7)	1.00
	3(27.3)	2(8.7)	0.30
	2(18.2)	2(8.7)	0.58
ıain	1(9.1)	3(13.0)	1.00
	0(0.0)	3(13.0)	0.53
	2(18.2)	0(0.0)	0.10
diagnosis			
ver episode	2(18.2)	3(13.0)	1.00
·potension episode	3(27.3)	2(8.7)	0.30
ıic episode[c]	0(0.0)	3(13.0)	0.53
	1(9.1)	0(0.0)	0.32
ıdings at diagnosis			
cell count (SD)	7900(3800)	6900(2300)	0.34
cell count (SD)	392(455)	272(290)	0.40
ium, mEq/dl (SD)	139(4)	132(13)	0.12
ssium, mEq/dl (SD)	3.9(0.6)	4.5(0.8)	0.04
ose, mg/dl (SD)	153(90)	90(26)	0.003
a due to SIADH atdiagnosis	0(0.0)	9(39.1)	0.02

[a]Values are expressed as thenumber with the percentage of the total number, unless otherwisestated.
[b]Comparisons of clinicalfeatures between patients who werediagnosed with glucocorticoid-induced AI and central AIdue to other causes were performed by using Fisher's exact test forcategorical variables and Student's t-test for continuousvariables.
[c]Only symptomatichypoglycaemic episodes that needed intervention wereincluded.
AI:adrenal insufficiency; ACTH: adrenocorticotropic hormone; SD:standard deviation; SIADH: syndrome of inappropriate secretion ofantidiuretic hormone.

Additional File Legends

Table S1. Disease lists corresponding toadrenal insufficiency and reasons for exclusions. [a]Ofthose, 9 cases were diagnosed for the same patients. Thus, a totalof 47 cases were newly diagnosed as adrenal insufficiency andtreated by hormone replacement during the study period.

Table S2. Baseline characteristics of the 34patients who were newly diagnosed with adrenal insufficiency.[a]Values are expressed as the number with the percentageof the total number, unless otherwise stated. [b]Onlysymptomatic hypoglycaemic episodes that needed intervention wereincluded.

Table S3. Results of tests for thehypothalamic-pituitary-adrenal axis and other hormones in the 34adrenal insufficiency patients. [a]Morning cortisol andACTH level.

[b]Plus indicates the presence of a response of thetarget organ in the hormone-stimulating tests, while minusindicates no response of the target organ in thehormone-stimulating tests. [c]Random cortisol level.

Figures

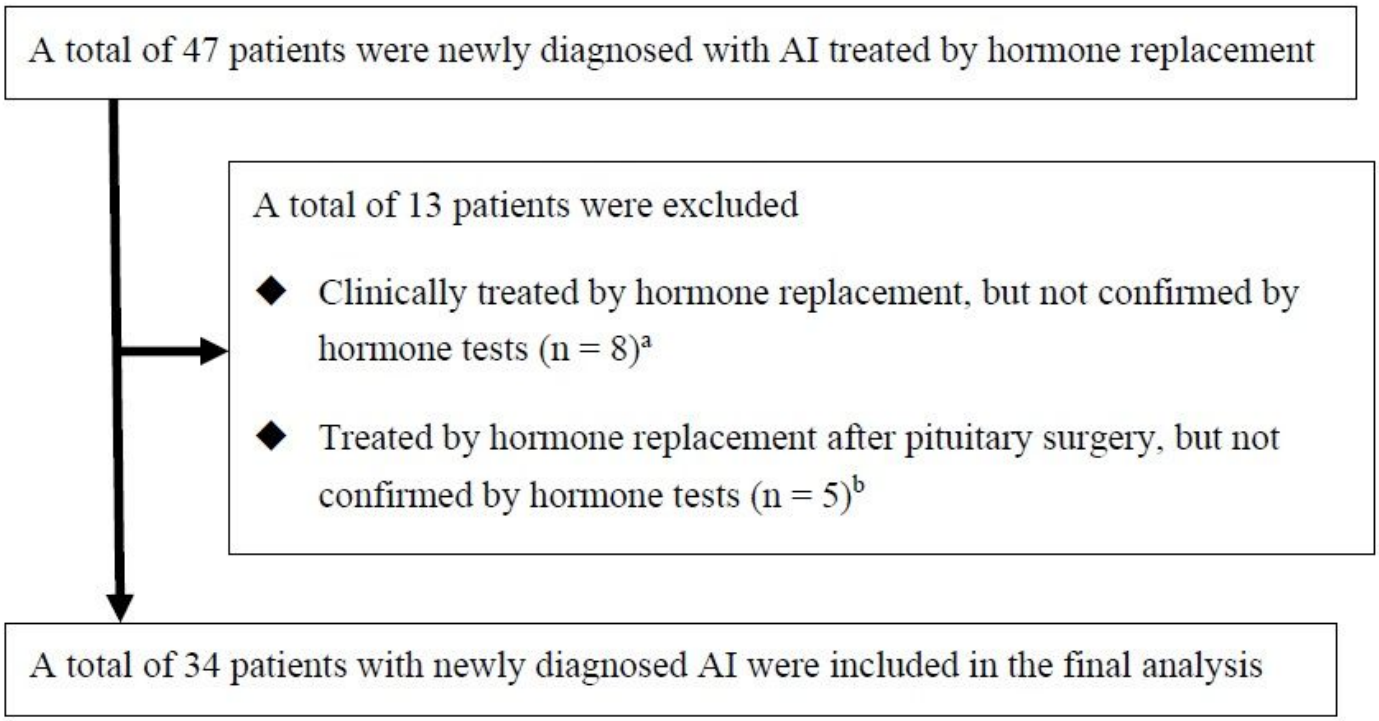

Figure 1

Flow chart of the 34 patients included in this study. aFive had glucocorticoid-induced adrenal insufficiency or critical illness-related corticosteroid insufficiency, and three had central adrenal insufficiency of unknown causes. bAll patients lacked symptoms associated with adrenal insufficiency. AI: adrenal insufficiency.

Supplementary Files

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