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Original Article

Epidemiology of adrenal insufficiency: A nationwide study of hospitalizations in Taiwan from 1996 to 2008

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Abstract

Background: Adrenal insufficiency (AI) is an uncommon but life-threatening disorder if it progresses to adrenal crisis. The nationwide trend of AI epidemiology in Taiwan has been infrequently reported.
Methods: Based on complete hospitalization datasets from the National Health Insurance Research Database, the trend of the annual incidence of AI from 1996 to 2008 in Taiwan was retrospectively analyzed. Special attention was paid to age-specific incidence, contributing factors as well as comorbidity at the time of AI diagnosis.
Results: Of the existing 35,884,231 hospitalization records, there were 52,660 with AI diagnosis in 32,085 patients (15,914 women and 16,163 men). The annual incidence of AI increased over time from $6.4/10^5$ ($n = 1280$) in 1996 to $15.2/10^5$ ($n = 3494$) in 2008. Nearly four-fifths (77%, $n = 24{,}688$) of the patients were aged at least 60 years at the time of their first AI diagnosis. The increase of the annual incidence of AI during the study period was largely attributed to disease prevalence in patients aged 60 years and over, with the most marked increase in the population aged 80 years of age from $51.1/10^5$ in 1996 to $179.9/10^5$ in 2008. Most patients with newly diagnosed AI were treated at internal medicine wards (81.1%, $n = 26{,}032$), at academic medical centers (51.9%, $n = 16{,}648$) and in southern Taiwan (54%, $n = 17{,}334$). The most common comorbidity was pneumonia (6.4%, $n = 2051$), followed by urinary tract infection (6.4%, $n = 2049$), diabetes mellitus (6.2%, $n = 1985$), electrolyte imbalance (4.8%, $n = 1551$), and chronic obstructive pulmonary disease (4.5%, $n = 1428$).
Conclusion: The annual incidence of AI in Taiwan had continuously increased in recent years, and elderly patients accounted for the majority of the increase. In the face of an increasingly aging population, Taiwanese physicians should pay more attention to this easily overlooked disease.

Keywords: adrenal insufficiency; comorbidity; epidemiology; Taiwan

1. Introduction

Adrenal insufficiency (AI) is uncommon but life-threatening if it progresses to adrenal crisis with electrolyte imbalance, change of consciousness or even shock. The causes of AI can be primary or secondary. Generally, the number of patients with secondary AI far exceeds that with primary AI.[1] Epidemiological surveys in Caucasian populations revealed that the prevalence of primary and secondary AI in the 1990s ($9-14/10^5$ and $15-28/10^5$ population respectively) were higher than those in the 1960s.[1,2] The reverse trend was observed in Japan where incidences of primary AI decreased from the 1960s to the 1990s.[3] In Taiwan, a recent study

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mentioned that the prevalence of AI among the elderly population has increased continuously since 1996.[4] However, the composition and causes of this increasing trend have not yet been studied in detail.

The aim of our current study is to analyze the 13-year trend of annual prevalence and incidence of AI from 1996 to 2008 in Taiwan by means of the complete nationwide insurance hospitalization claims records. Special attention was paid to age-specific incidence, contributing factors as well as comorbidity at AI diagnosis.

2. Methods

The complete datasets of hospitalizations (inpatient expenditures by admissions) were obtained from the National Health Insurance (NHI) Research Database at the National Health Research Institutes in Miaoli, Taiwan.[5] A total of 35,884,231 records exist from 1996 to 2008. Each record of these datasets contains the patient's identification number, gender, date of birth, dates of admission and discharge, up to five discharge diagnoses coded in the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) format, and the identification number of the medical care facility. For privacy protection, the original identification numbers of patients and medical care facilities were scrambled cryptographically to ensure anonymity.

In the current study, patients with AI were identified according to the discharge diagnoses (255.4 in ICD-9-CM). From the data of all patients with treated AI, their first hospitalizations with an AI diagnosis during the study period were selected for incidence estimation and further analysis. Because the NHI program was started in 1995 and only electronic claims data after 1996 were available, a consistent definition in calculating the incidences over the 10 years was not warranted. The incidence of the first few years might have been underestimated. For each first hospitalization, the specialty and hospital were extracted. In calculation, the specialties were classified into officially recognized major specialties. A medical care facility in each hospitalization record was linked to the registry file of medical care facilities (HOSB2008.DAT) to identify its contracted category and location. The contracted category includes academic medical center, metropolitan hospital, local community hospital or primary care clinic. The facility locations were also separated into groups, which included Taipei, Northern, Central, Southern, Kao-Ping, or Eastern Branches of the Bureau of NHI.

To analyze the comorbidity of new AI cases, the first discharge diagnosis was extracted from the hospitalization records in which AI was newly diagnosed. If AI was the primary diagnosis, the second discharge diagnosis would be extracted instead. The Clinical Classification Software (CCS) 2010 version[6] was used to classify diagnoses into a manageable number of clinically meaningful categories with 295 single-level diagnostic groups.

2.1. Statistical analysis

Annual numbers of beneficiaries were obtained from the official website of the Bureau of NHI[5] to serve as denominators in calculating the annual prevalence and incidence. Age-specific incidence was determined in every age group in increments of 20 years. From the nonsampled population datasets, descriptive statistics were presented. All calculations were performed with Perl software version 5.12.1.[7]

3. Results

3.1. Prevalence

From 35,884,231 hospitalization records between 1996 and 2008, 52,660 records with AI diagnosis were identified in 32,085 patients (15,914 women and 16,163 men). The annual prevalence of treated AI gradually increased from $6.4/10^5$ ($n = 1280$) in 1996 to $20.0/10^5$ ($n = 4591$) in 2008 (Fig. 1).

3.2. Incidence and patients' characteristics

Similarly, the annual incidence of AI increased from $6.4/10^5$ ($n = 1,280$) in 1996 to $15.2/10^5$ ($n = 3494$) in 2008 (Fig. 1). The incidences did not differ remarkably between both sexes: from $6.5/10^5$ in 1996 to $14.8/10^5$ in 2008 in women vs. an increase from $6.3/10^5$ in 1996 to $15.8/10^5$ in 2008 in men. Nearly four-fifths (77%, $n = 24,688$) of the patients aged 60 years and over at the time of their first AI diagnosis (Table 1). The mean age was 67.3 ± 15.2 years: 67.2 ± 15.0 years in women and 67.4 ± 15.4 years in men. The increase of annual incidences during the study period was largely attributed to the patients aged at least 60 years (Table 1). The increasing trend was most marked in the population aged 80 years and over: from $51.1/10^5$ in 1996 to $179.9/10^5$ in 2008 (Fig. 2).

3.3. Specialty and hospital in which AI was newly diagnosed

The records showed that four-fifths of the patients with newly diagnosed AI were treated at internal medicine wards

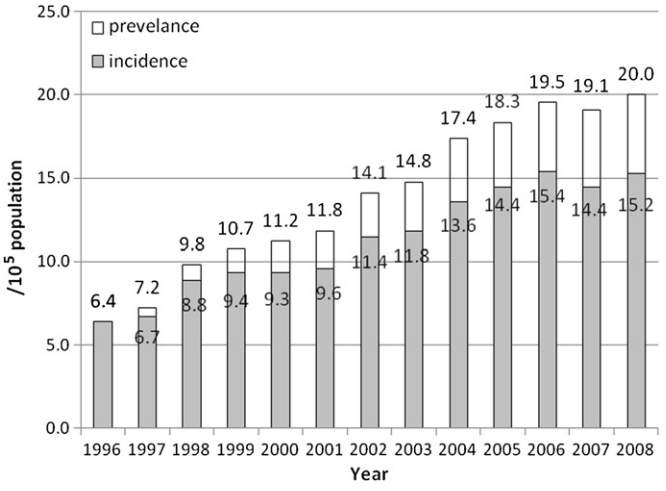

Fig. 1. Annual prevalence and incidence of adrenal insufficiency, 1996–2008.

Table 1
Characteristics of the patients at the first diagnosis of adrenal insufficiency, 1996–2008, *n* (%).

	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Sex													
Female	646 (50.5)	696 (50.9)	962 (52.4)	981 (49.7)	1016 (50.8)	1089 (52.5)	1245 (49.8)	1270 (49.0)	1459 (48.5)	1590 (49.4)	1693 (49.0)	1575 (47.9)	1692 (48.4)
Male	634 (49.5)	672 (49.1)	875 (47.6)	990 (50.2)	983 (49.2)	984 (47.4)	1253 (50.1)	1319 (50.9)	1548 (51.5)	1630 (50.6)	1760 (51.0)	1713 (52.1)	1802 (51.6)
Unknown	0	0	0	1	1	1	2	2	1	0	0	0	0
Age group													
0–19	27 (2.1)	30 (2.2)	32 (1.7)	41 (2.1)	30 (1.5)	24 (1.2)	28 (1.1)	47 (1.8)	38 (1.3)	38 (1.2)	40 (1.2)	37 (1.1)	44 (1.3)
20–39	61 (4.8)	67 (4.9)	92 (5.0)	97 (4.9)	78 (3.9)	93 (4.5)	93 (3.7)	93 (3.6)	126 (4.2)	116 (3.6)	128 (3.7)	160 (4.9)	130 (3.7)
40–59	301 (23.5)	298 (21.8)	363 (19.8)	399 (20.2)	354 (17.7)	355 (17.1)	445 (17.8)	437 (16.9)	480 (16.0)	516 (16.0)	543 (15.7)	521 (15.8)	595 (17.0)
60–79	775 (60.5)	828 (60.5)	1138 (61.9)	1191 (60.4)	1273 (63.7)	1285 (62.0)	1495 (59.8)	1574 (60.7)	1803 (59.9)	1860 (57.8)	1964 (56.9)	1760 (53.5)	1778 (50.9)
80+	116 (9.1)	145 (10.6)	212 (11.5)	244 (12.4)	265 (13.3)	317 (15.3)	439 (17.6)	440 (17.0)	561 (18.7)	690 (21.4)	778 (22.5)	810 (24.6)	947 (27.1)
Hospital type													
Academic medical center	632 (49.4)	767 (56.1)	1142 (62.2)	1203 (61.0)	1186 (59.3)	1218 (58.7)	1428 (57.1)	1368 (52.8)	1575 (52.4)	1561 (48.5)	1637 (47.4)	1428 (43.4)	1503 (43.0)
Metropolitan hospital	444 (34.7)	437 (31.9)	501 (27.3)	543 (27.5)	591 (29.6)	614 (29.6)	773 (30.9)	962 (37.1)	1159 (38.5)	1381 (42.9)	1447 (41.9)	1463 (44.5)	1561 (44.7)
Local hospital	204 (15.9)	164 (12.0)	194 (10.6)	226 (11.5)	223 (11.2)	242 (11.7)	299 (12.0)	261 (10.1)	274 (9.1)	278 (8.6)	369 (10.7)	397 (12.1)	430 (12.3)
Hospital location													
Taipei	245 (19.1)	267 (19.5)	315 (17.1)	340 (17.2)	349 (17.5)	322 (15.5)	401 (16.0)	377 (14.6)	389 (12.9)	467 (14.5)	669 (19.4)	558 (17.0)	610 (17.5)
Northern	270 (21.1)	285 (20.8)	430 (23.4)	453 (23.0)	399 (20.0)	407 (19.6)	465 (18.6)	507 (19.6)	580 (19.3)	501 (15.6)	582 (16.9)	491 (14.9)	482 (13.8)
Central	156 (12.2)	190 (13.9)	198 (10.8)	232 (11.8)	190 (9.5)	177 (8.5)	179 (7.2)	203 (7.8)	263 (8.7)	247 (7.7)	280 (8.1)	320 (9.7)	372 (10.6)
Southern	217 (17.0)	173 (12.6)	151 (8.2)	267 (13.5)	320 (16.0)	389 (18.8)	575 (23.0)	740 (28.6)	799 (26.6)	952 (29.6)	906 (26.2)	951 (28.9)	1132 (32.4)
Kao-Ping	358 (28.0)	414 (30.3)	716 (39.0)	652 (33.1)	706 (35.3)	741 (35.7)	840 (33.6)	727 (28.1)	919 (30.6)	983 (30.5)	949 (27.5)	910 (27.7)	847 (24.2)
Eastern	34 (2.7)	39 (2.9)	27 (1.5)	28 (1.4)	36 (1.8)	38 (1.8)	40 (1.6)	37 (1.4)	58 (1.9)	70 (2.2)	67 (1.9)	58 (1.8)	51 (1.5)
Specialty (selected)													
Internal medicine	1057 (82.6)	1140 (83.3)	1530 (83.3)	1622 (82.3)	1620 (81.0)	1699 (81.9)	1974 (79.0)	2098 (81.0)	2382 (79.2)	2584 (80.2)	2820 (81.7)	2661 (80.9)	2845 (81.4)
Neurology	62 (4.8)	72 (5.3)	75 (4.1)	93 (4.7)	94 (4.7)	80 (3.9)	100 (4.0)	151 (5.8)	146 (4.9)	188 (5.8)	169 (4.9)	158 (4.8)	170 (4.9)
Surgery	60 (4.7)	52 (3.8)	94 (5.1)	93 (4.7)	111 (5.6)	100 (4.8)	185 (7.4)	125 (4.8)	191 (6.3)	218 (6.8)	217 (6.3)	185 (5.6)	180 (5.2)
Orthopedics	48 (3.8)	40 (2.9)	55 (3.0)	64 (3.2)	71 (3.6)	111 (5.4)	145 (5.8)	99 (3.8)	141 (4.7)	99 (3.1)	107 (3.1)	122 (3.7)	99 (2.8)
Neurosurgery	4 (0.3)	9 (0.7)	11 (0.6)	18 (0.9)	25 (1.3)	23 (1.1)	20 (0.8)	30 (1.2)	35 (1.2)	43 (1.3)	49 (1.4)	72 (2.2)	96 (2.7)
Pediatrics	19 (1.5)	20 (1.5)	25 (1.4)	36 (1.8)	20 (1.0)	19 (0.9)	18 (0.7)	33 (1.3)	36 (1.2)	30 (0.9)	26 (0.8)	32 (1.0)	31 (0.9)

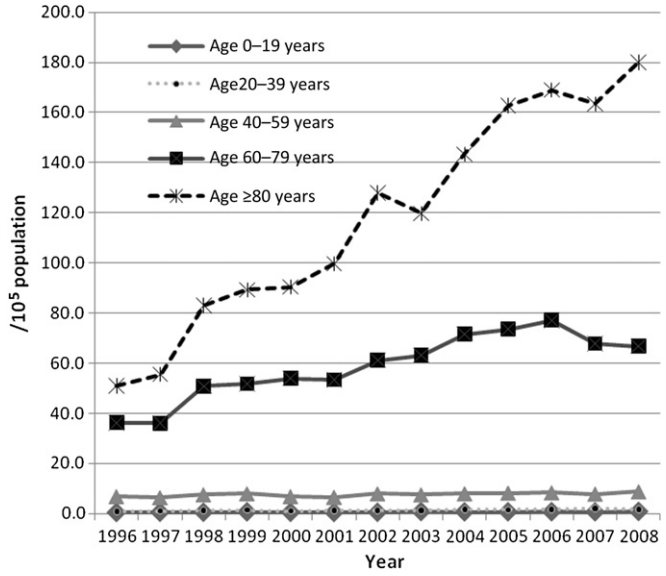

Fig. 2. Annual age-specific incidence of adrenal insufficiency, 1996–2008.

(n = 26,032), followed by those of neurology (n = 1811) and surgery (n = 1558) (Table 1). More than 50% of patients were treated at academic medical centers (n = 16,648) and in southern Taiwan (Southern and Kao-Ping branches, n = 17,334). During the study period, internal medicine facilities continued to play a major role in AI diagnosis: from 82.6% (n = 1057) of all new patients in 1996 to 81.4% (n = 2845) in 2008. As to hospitals, cases of newly diagnosed AI at metropolitan hospitals had markedly increased over time and even outnumbered those at academic medical centers since 2007 (1463 patients vs. 1428 in 2007 and 1561 vs. 1503 in 2008). The hospitals in southern Taiwan (Southern and Kao-Ping branches) had not only the most new cases each year but also the most prominent elevating trend: from 575 patients in 1996 to 1979 in 2008.

3.4. Comorbidities

Of hospitalizations with newly diagnosed AI in the 13-year period we reviewed, only 151 patients (0.5%) had AI as the sole diagnosis upon discharge. The most common comorbidity was pneumonia (6.4%, n = 2051), followed by urinary tract infection (6.4%, n = 2049), diabetes mellitus (6.2%, n = 1985), electrolyte imbalance (4.8%, n = 1551), and chronic obstructive pulmonary disease (4.5%, n = 1428; Table 2). The top 10 diagnostic groups accounted for almost 50% (45%, n = 14,454) of all comorbidities. After comparison of the first and last year of the study period, the infection-related comorbidities had the most prominent increasing trends: pneumonia (16.5 times), septicemia (6.4 times), and urinary tract infection (4.5 times).

4. Discussion

AI may occur as a result of a wide variety of diseases. Common causes of primary AI include autoimmune disease,

Table 2
Comorbidities at the first diagnosis of adrenal insufficiency, 1996–2008, n (%).

	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Pneumonia (except that caused by tuberculosis or sexually transmitted disease)	21 (1.6)	55 (4.0)	48 (2.6)	86 (4.4)	77 (3.9)	87 (4.2)	130 (5.2)	159 (6.1)	220 (7.3)	254 (7.9)	267 (7.7)	301 (9.2)	346 (9.9)
Urinary tract infections	59 (4.6)	71 (5.2)	116 (6.3)	110 (5.6)	117 (5.9)	134 (6.5)	144 (5.8)	206 (8.0)	191 (6.3)	218 (6.8)	219 (6.3)	197 (6.0)	267 (7.6)
Diabetes mellitus with complications	94 (7.3)	100 (7.3)	200 (10.9)	162 (8.2)	158 (7.9)	145 (7.0)	162 (6.5)	191 (7.4)	144 (4.8)	158 (4.9)	173 (5.0)	145 (4.4)	153 (4.4)
Fluid and electrolyte disorders	45 (3.5)	42 (3.1)	48 (2.6)	76 (3.9)	81 (4.1)	87 (4.2)	113 (4.5)	130 (5.0)	158 (5.3)	147 (4.6)	216 (6.3)	211 (6.4)	197 (5.6)
Chronic obstructive pulmonary disease and bronchiectasis	47 (3.7)	54 (3.9)	71 (3.9)	86 (4.4)	86 (4.3)	81 (3.9)	142 (5.7)	133 (5.1)	165 (5.5)	153 (4.8)	140 (4.1)	128 (3.9)	142 (4.1)
Skin and subcutaneous tissue infections	36 (2.8)	49 (3.6)	81 (4.4)	90 (4.6)	101 (5.1)	92 (4.4)	130 (5.2)	130 (5.0)	120 (4.0)	144 (4.5)	161 (4.7)	129 (3.9)	142 (4.1)
Septicemia (except in labor)	31 (2.4)	36 (2.6)	55 (3.0)	60 (3.0)	45 (2.3)	72 (3.5)	73 (2.9)	81 (3.1)	126 (4.2)	150 (4.7)	187 (5.4)	187 (5.7)	199 (5.7)
Other endocrine disorders	135 (10.5)	107 (7.8)	115 (6.3)	103 (5.2)	107 (5.4)	104 (5.0)	106 (4.2)	79 (3.0)	84 (2.8)	84 (2.6)	100 (2.9)	87 (2.6)	73 (2.1)
Acute cerebrovascular disease	32 (2.5)	27 (2.0)	41 (2.2)	44 (2.2)	45 (2.3)	47 (2.3)	72 (2.9)	53 (2.0)	84 (2.8)	79 (2.5)	76 (2.2)	70 (2.1)	86 (2.5)
Gastrointestinal hemorrhage	26 (2.0)	29 (2.1)	47 (2.6)	35 (1.8)	48 (2.4)	49 (2.4)	47 (1.9)	55 (2.1)	48 (1.6)	66 (2.0)	75 (2.2)	48 (1.5)	70 (2.0)
Others	754 (58.9)	798 (58.3)	1015 (55.3)	1120 (56.8)	1135 (56.8)	1176 (56.7)	1381 (55.2)	1374 (53.0)	1668 (55.5)	1767 (54.9)	1839 (53.3)	1785 (54.3)	1819 (52.1)
Total	1280	1368	1837	1972	2000	2074	2500	2591	3008	3220	3453	3288	3494

infection, tumor, hemorrhage, and genetic disorders. Secondary AI is often related to pituitary lesion *per se* or hypothalamic−pituitary−adrenal axis suppression caused by critical illness or long-term use of steroid.[1] Although worldwide estimates of the incidence of secondary AI vary considerably.[8,9] growing numbers of primary cause AI patients have been observed in the Western population between the 1960s and the 1990s.[2] In our study covering a span of 13 years, the incidence of AI of all causes increased from 6.4 to 15.2/10^5. The increasing trend would be steeper because cases in the early years might include patients who had been diagnosed with AI before 1996. The increase might be attributed to an aging population, improving diagnostic ability as well as changing incidences of underlying diseases.

In our study, most patients were between the ages of 60 years and 80 years at their first hospitalization with an AI diagnosis. Studies in other countries showed the peak age at diagnosis was in the 4th decade of life in primary AI and the 6th decade in secondary AI.[1] Although we could not differentiate between primary and secondary AI in our study, the increasing trend of AI incidence in Taiwan can probably be attributed to the growing number of secondary AI cases in that the elderly population had the most marked increase in the number of patients and incidence.

In the literature, the type and locality of hospitals in which AI was treated had seldom been studied. In our study, nearly 90% of AI patients were first diagnosed in academic medical centers and metropolitan hospitals. The number of AI patients treated at metropolitan hospitals increased markedly over time and even exceeded that number treated at academic medical centers. In the meantime, the number of newly diagnosed AI patients also markedly increased at hospitals in southern Taiwan. These facts might imply that these hospitals have a higher level of ability to diagnose AI. The lower number of AI patients at local community hospitals might just reflect the possibility that critically ill patients are rarely treated there. In our study, most AI patients were treated in the internal medicine wards. The reason might be that AI predominantly resulted from medical illnesses such as autoimmune disorder and infection. Another reason might be that some patients of AI resulting from surgical procedures were transferred to the internal medicine wards during hospitalization. However, the NHI records cannot provide sufficient clues for the latter situation.

In our study, AI was seldom the sole diagnosis in hospitalized patients. Among all comorbidities of AI, the number of patients with infectious and pulmonary diseases increased disproportionately in comparison to AI incidences within the study period. The role of infectious stress in AI has been well-studied.[10−12] A recent study in Germany revealed that infectious diseases can trigger adrenal crises in patients with chronic AI.[13] Some studies also found that a high proportion of patients with severe community-acquired pneumonia or sepsis had AI.[11,12] The close relationship between adrenal function and the severity of community-acquired pneumonia has also been reported in Japan.[14] Another major comorbidity, electrolyte imbalance, is one of the alert signs of AI.[15] Although AI is an uncommon cause of hyponatremia,[16] it has been found that hyponatremia may be observed in approximately 80% of acute adrenal crises.[17] In our study, only 4.8% patients with first diagnosed AI had electrolyte imbalance. This comparatively low percentage might suggest that the severity of AI of most hospitalized patients in Taiwan does not reach the crisis level. Furthermore, a recent study disclosed that concomitant diabetes mellitus might increase the frequency of adrenal crises among patients with chronic AI.[18] In our study, diabetes mellitus and other endocrine diseases do not seem to have relationship with the increase of AI incidence.

There were some limitations in our study. Only the datasets of hospitalizations were available for analysis. The incidence might have been underestimated because those unrecognized or treated only in an ambulatory setting were not included in our study. We could not differentiate the primary and secondary causes of AI because they share the same coding in ICD-9-CM. Moreover, our datasets did not provide any laboratory results or drug prescriptions so that the severity of AI could not be known. Similarly, because the extent of prior patient medication before admission was unknown, we could not clarify the influence of therapeutic glucocorticoid administration on the development of AI. Finally, because any attempt to link the patients within the NHIRD to their original medical records is not permitted, the cause-and-effect relationships between AI and comorbidities could not be ascertained.

In conclusion, the annual incidence of AI in Taiwan had continuously increased in recent years, and elderly patients accounted for the majority of the increase. In the face of an aging population, Taiwanese physicians should become more aware of the clinical signs and symptoms of AI, thereby giving this easily overlooked and increasingly prevalent disease the attention it deserves.

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