

# Associations between different forms of gastro-oesophageal reflux disease

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## Abstract

**Aims**—To study the epidemiology and natural history of gastro-oesophageal reflux disease (GORD).

**Methods**—Retrospective cohort study involving all 172 hospitals of the Department of Veterans Affairs. A total of 194 527 patients with GORD were followed between 1981 and 1994. Distribution of oesophagitis, oesophageal ulcer, oesophageal stricture, strictured hiatus hernia, hiatus hernia, and pyrosis by age, sex, and ethnicity were determined. The comorbid occurrence of various forms of GORD in identical patients was analysed by an age and race standardised morbidity ratio. The population of all hospitalised veterans was used for comparison.

**Results**—Severe forms of GORD associated with oesophageal erosions, ulcers, or strictures, affected elderly, white, male patients more often than their corresponding opposite demographic group. All forms of GORD clustered in the same patient population; on average, any form of GORD was 10 times more likely to occur in a patient with another form of GORD than without. The highest morbidity ratio (22) was found in oesophageal ulcer and stricture. About one third of all patients with oesophageal erosions, ulcers, or strictures also had hiatus hernia; 46% of patients with hiatus hernia were diagnosed as having other forms of GORD. While one third of all oesophageal strictures appeared in patients without other forms of GORD diagnosed at any time, oesophageal ulcers were always associated with some other form of GORD. No clear cut progression in different forms of GORD was found.

**Conclusions**—Older age, male sex, and white ethnicity are risk factors in the development of severe forms of GORD. The most severe grade of GORD is reached at the onset of the disease.

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**Keywords:** epidemiology of GORD; erosive oesophagitis; oesophageal stricture; oesophageal ulcer; hiatus hernia; natural history; pyrosis; reflux oesophagitis

Gastro-oesophageal reflux disease (GORD) is a common chronic disorder that results from the retrograde flow of gastric contents into the oesophagus. It encompasses a broad clinical spectrum that ranges from regurgitation, pyrosis, and epigastric pain without endoscopic

lesions to severe erosive oesophagitis accompanied by various complications, such as oesophageal ulcers, strictures, and Barrett's metaplasia. In all classifications of GORD, its severity is graded by the extent of the erosions and the occurrence of complications.<sup>1-3</sup> The comorbid association among the various forms of GORD and their temporal progression are not however fully understood. Several studies have followed the long term course of GORD.<sup>4-9</sup> It is evident from these studies that GORD is a chronic disease with little spontaneous resolution and frequent relapses. Out of fear that untreated GORD might progress from mild to more severe and complicated forms, physicians are advised to treat the disease vigorously and patients are cautioned to adhere to the prescribed regimens.<sup>10</sup> Very few investigators were able to observe transitions between different grades of severity of GORD.<sup>9 11 12</sup> The Patient Treatment File (PTF) of the Department of Veterans Affairs (VA) is comprised of the computerised records of all inpatients treated in all VA hospitals throughout the United States since 1970. Such a database offers the unique opportunity to study a large number of patients with GORD over prolonged time periods. In the present study, we used this database to shed light on the epidemiology and natural history of GORD. We were particularly interested in the comorbid occurrences of various forms of GORD and their temporal relationships.

## Methods

### DATA SOURCE

The PTF served as the data source for the present study. The computerised data files contain the records of all inpatients from all 172 VA hospitals distributed throughout the United States. The PTF is managed by the VA Central Automation Center in Austin, Texas. It was started in 1970, and files are available for each fiscal year since then. Each annual file contains the records of about one million hospitalisations among more than 600 000 US military veterans. Individual patients can be identified by their unique social security number. In addition to demographic characteristics, each patient's record contains one primary and up to nine secondary discharge diagnoses. Since 1981, the discharge diagnoses were encoded according to the ninth revision of the Clinical Modification of the International Classification of Diseases (ICD).<sup>13</sup> Accredited record technicians extract the diagnoses from the original discharge record and translate them into ICD codes.

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TABLE 1 Age of patients with various forms of GORD

ICD code	GORD form	n	Age (years)	SD
	VA population	3411453	57.5	NA
530.1	Oesophagitis	108397	60.6	12.6
530.2	Oesophageal ulcer	16011	62.2	11.9
530.3	Oesophageal stricture	22507	64.2	10.8
552.3	Strictured hiatus hernia	1049	62.9	12.4
553.3	Hiatus hernia	104356	61.5	12.3
787.1	Pyrosis	1773	61.9	11.6

Source: patient treatment files 1981–94.

#### DATA EXTRACTION

Patients with GORD were identified as inpatients discharged from the VA hospitals between 1981 and 1994 with any of the following primary or secondary diagnoses: erosive oesophagitis (ICD code 530.1), oesophageal ulcers (ICD code 530.2), oesophageal strictures (ICD code 530.3), strictured hiatus hernia (ICD code 552.3), hiatus hernia (ICD code 553.3), or pyrosis (ICD code 787.1). To ensure that only cases with a GORD related diagnosis were considered, patients with any discharge diagnosis of infectious, radiation induced, or caustic oesophagitis were excluded from the case population. Similarly, patients with any benign or malignant neoplasm of the larynx, hypopharynx, oesophagus, and stomach were excluded. The population of all hospitalised veterans between 1981 and 1993 was used for comparison.

For every subject, demographic data including sex, ethnicity, and age at the time of first appearance in the PTF were extracted from the database. In all patients with GORD, the first

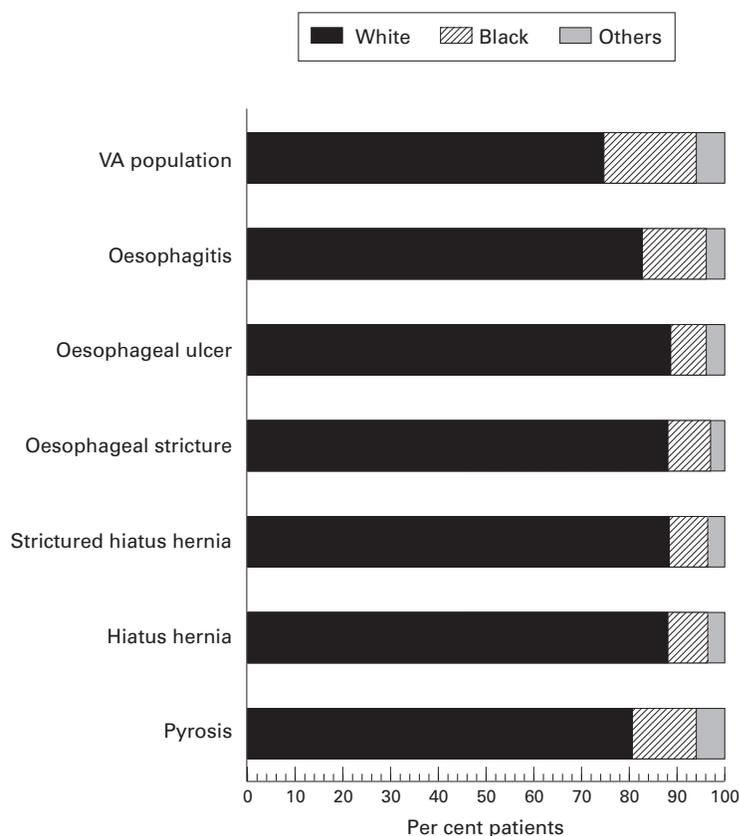


Figure 1: The ethnic distribution of the hospitalised veteran population and patients with various forms of GORD.

admission date for any given form of GORD was recorded. The comorbid occurrences of each two of the six forms of GORD in identical subjects were analysed using the PROC TABULATE of SAS to create a six by six table.<sup>14</sup> The temporal associations between each two forms of GORD were analysed by breaking their total number of comorbid occurrences into those with the one form of GORD occurring before, simultaneously, or after the second form. Any two forms of GORD were considered to have occurred simultaneously, if the two diagnoses were made within a 14 day period.

#### STATISTICAL ANALYSES

The mean age of patients with a given form of GORD and the mean age of the population of all hospitalised veterans were compared using Student's *t* test. The race and sex distributions of patients with a given form of GORD were compared with the corresponding distributions of the veterans population, using the  $\chi^2$  test with one degree of freedom.<sup>15</sup> In both types of comparison, the population value represented the standard or expected value. The multiple  $\chi^2$  test was used to test whether the temporal sequence of each two forms of GORD differed from the expected uniform distribution "before" and "after". Yates's continuity correction was used for all  $\chi^2$  tests.

Comorbidity was calculated as an age and race standardised morbidity ratio (R) of observed to expected numbers of patients with two forms of GORD.<sup>16</sup> The expected number (EXP) of patients with a given comorbidity was calculated by applying the rates of the first form to the population of the second form. For example, the expected number of cases with oesophagitis (oeso) and oesophageal ulcers (ulc) was:

$$EXP_{\text{oeso.ulc}} = (POP_{\text{oeso}}/POP_{\text{vet}}) \times POP_{\text{ulc}}$$

where  $POP_{\text{vet}}$  is the total population of hospitalised veterans between 1981 and 1993. The expected number of associations was calculated for each age and race group separately and then added up. The ratio  $R = \text{OBS}:\text{EXP}$  measured the strength of the association between each two diagnoses. The significance of the strength of the associations was tested with  $\chi^2$  tests comparing the observed with the expected value.

#### Results

In the time period 1981 to 1994, 194 527 patients were discharged from VA hospitals with various diagnoses of GORD. Their demographic characteristics were compared with those of all hospitalised veterans. Table 1 shows the average age and the contribution of each diagnosis to the total GORD population among US veterans. Erosive oesophagitis comprised 45.4% of the total GORD population, while oesophageal ulcers occurred in 6.0% and oesophageal strictures in 8.4%. Hiatus hernia was diagnosed in 39.1% of the total GORD population. Pyrosis and strictured hiatus hernia were both listed as discharge diagnoses in

TABLE 2 Comorbid associations among various forms of GORD

Condition	Oesophagitis	Oesophageal ulcer	Oesophageal stricture	Strictured hiatus hernia	Hiatus hernia	Pyrosis
Oesophagitis						
Oesophageal ulcer	7850					
Oesophageal stricture	8498	2900				
Strictured hiatus hernia	364	61	164			
Hiatus hernia	37013	5437	6253	400		
Pyrosis	443	32	37	3	335	
Total	108397	16011	22507	1049	104356	1773

TABLE 3 Ratios of observed over expected comorbid associations among various forms of GORD

Condition	Oesophagitis	Oesophageal ulcer	Oesophageal stricture	Strictured hiatus hernia	Hiatus hernia	Pyrosis
Oesophagitis						
Oesophageal ulcer	12.96					
Oesophageal stricture	9.86	21.85				
Strictured hiatus hernia	9.19	10.09	18.68			
Hiatus hernia	9.41	9.11	7.34	10.21		
Pyrosis	7.20	3.63	3.13	5.26	5.74	

less than 1% of the GORD population. Compared with the general hospitalised veterans population, patients with GORD were significantly older ( $p < 0.001$ ). Patients with oesophageal ulcers or strictures were older than patients with uncomplicated oesophagitis. The hospitalised veteran population was mainly comprised of male patients, only 2.3% being women. By comparison, 1.9% and 2.3% patients with oesophagitis and hiatus hernia, respectively, were women. Female rates were halved in patients with oesophageal ulcers (1.2%,  $p < 0.001$ ) or oesophageal strictures (1.4%,  $p < 0.001$ ) as compared with the entire

population. Figure 1 illustrates the ethnic distribution of patients with various forms of GORD. Compared with the adult US population, the population of hospitalised veterans contains a relatively large fraction of non-whites. All forms of GORD, however, were characterised by a significantly smaller fraction of non-whites than the VA population. Among patients with GORD, patients with complications of GORD were characterised by particularly low fractions of non-whites.

Table 2 shows the numbers of comorbid associations among different forms of GORD. These numbers provide an estimate for the strength of the association between each two diagnoses. For example, a comorbid occurrence of oesophagitis with oesophageal ulcer was observed in 7850 subjects. Using the above formula, the expected value is:

$$EXP_{\text{oeso,ulc}} = (POP_{\text{oeso}}/POP_{\text{vet}}) \times POP_{\text{ulc}} = (108\,397/3\,411\,000) \times 16\,011 = 509.$$

The ratio OBS:EXP = 7850/509 = 15.4 is higher than the value 13.0 given in table 3 for the same association. The difference between the two values reflects the influence of adjusting the ratios to the age and race distribution of all hospitalised veterans. The majority of ratios were close to  $R=10$ . The weakest associations were found in pyrosis. All other associations were statistically significant at a level of  $p < 0.0001$ . The strongest association was observed between oesophageal ulcers and strictures. Figure 2 shows the comorbid association between forms of GORD, the analysis being restricted to the four most common forms of GORD. The four arrows emanating from each shaded area, representing one form of GORD, add up to 100% except for rounding errors. For example, erosive oesophagitis, the most frequently diagnosed form of GORD, was the sole diagnosis in 51% of patients with this condition. About one third of all patients with oesophageal erosions, ulcers, or strictures had a concomitant hiatus hernia. On the other hand, 47% of patients with hiatus hernia were diagnosed to have another form of GORD, erosive oesophagitis being the most frequent. While 22% of all oesophageal

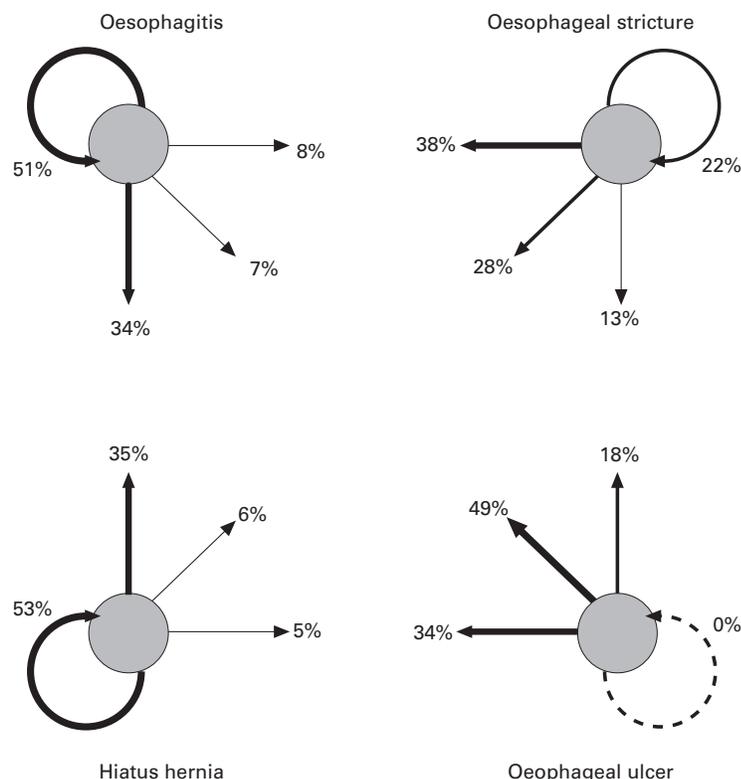


Figure 2: Comorbid associations between four forms of GORD, each arrow representing one association. The percentage describes the fraction of patients with one form of GORD (where the arrow starts) who also suffer from a second form (to which the arrow points). The circular arrows represent patients who have one form of GORD as their sole presentation.

TABLE 4 Temporal relationships between each of two forms of GORD

Form of GORD [1]	[1] before [2]	Simultaneous	[1] after [2]	Form of GORD [2]
Oesophagitis	1752(22%)	3039(39%)	3059(39%)	Oesophageal ulcer
Oesophagitis	2500(29%)	3721(44%)	2277(27%)	Oesophageal stricture
Oesophagitis	106(29%)	132(36%)	126(35%)	Strictured hiatus hernia
Oesophagitis	6993(19%)	21789(59%)	8231(22%)	Hiatus hernia
Oesophagitis	150(34%)	187(42%)	106(24%)	Pyrosis
Oesophageal ulcer	659(23%)	1180(41%)	1061(37%)	Oesophageal stricture
Oesophageal ulcer	20(33%)	13(21%)	28(46%)	Strictured hiatus hernia
Oesophageal ulcer	1210(22%)	2288(42%)	1939(36%)	Hiatus hernia
Oesophageal ulcer	11(34%)	6(19%)	15(47%)	Pyrosis
Oesophageal stricture	69(42%)	51(31%)	44(27%)	Strictured hiatus hernia
Oesophageal stricture	1984(32%)	2777(44%)	1492(24%)	Hiatus hernia
Oesophageal stricture	14(38%)	9(24%)	14(38%)	Pyrosis
Strictured hiatus hernia	167(42%)	9(2%)	224(56%)	Hiatus hernia
Strictured hiatus hernia	2(67%)	0(0%)	1(33%)	Pyrosis
Hiatus hernia	145(43%)	91(27%)	99(30%)	Pyrosis

strictures appeared in patients without other forms of GORD diagnosed at any time, oesophageal ulcers were always associated with some other form of GORD.

Of 194 527 patients with GORD, 23 625 were followed for a time period of more than one year. Their average length of follow up was 2.68 years (SD 2.71 years) with an average of 2.1 hospital discharges (SD 0.4) per patient. Table 4 shows the temporal relationships between the various forms of GORD. They are expressed as the number (and percentage) of each of two ICD codes, with the first code occurring before, simultaneously, or after the second one. Secondary to the large size of most samples, the  $\chi^2$  tests were statistically significant when the observed distribution between "before" and "after" was compared with an expected equal distribution. Only a few of the distributions involving pyrosis and strictured hiatus hernia were not found to be statistically significant. On the other hand, no consistent pattern could be discerned. In some relationships, it appeared as if less severe forms precede the more severe ones. For example, hiatus hernia tended to precede oesophageal erosions or ulcers. Similarly, oesophagitis was diagnosed slightly more often before oesophageal strictures. However, appreciable numbers of severe and mild forms of GORD presented simultaneously or with the severe form before the mild one. For example, in the comorbid occurrence of oesophagitis, oesophageal ulcer represented the initial diagnosis in 39%, whereas oesophagitis represented the initial diagnosis in only 22%. The definition of a "simultaneous" occurrence of two forms of GORD was changed between "two forms being diagnosed on the same date" and "two forms being diagnosed within 14 days". Such variations in the definition affected the distributions of Table 4 only slightly and did not lead to any pattern that was different from the one shown.

### Discussion

The present study deals with different forms of GORD in all patients discharged from the 172 VA hospitals in the United States. The natural history of GORD was followed in 195 000 patients over a 14 year period. Their data were stored using the International Classification of Diseases, which contains six separate diagnostic codes to represent the clinical spectrum of GORD. Our results showed that severe forms

of GORD tended to affect primarily older male patients of white ethnicity. Besides the fact that all forms of GORD clustered in the same patient population, the association between oesophageal ulcers and strictures stood out as being particularly strong. No clear temporal sequence between various forms of GORD could be appreciated.

In relying on the computerised data file of the Department of Veterans Affairs for analysing the natural history of GORD, it is important to address several shortcomings of this large database. The database contains no data on the history of the disease before it became recorded during the first hospitalisation. An individual patient might have experienced a period of reflux symptoms and self medication, before he/she came to medical attention. Since the database does not include pharmacy data, we were unable to assess the influence of various types of antisecretory therapy on the course of the disease. The data were collected over a long time period by many physicians from different medical centres. While there was probably less variation in the diagnostic definition of strictures or ulcers, the occurrences of hiatus hernia or oesophagitis could have been subject to observer error. Finally, US military veterans tend to be of lower socioeconomic status with heavy tobacco and alcohol consumption. These characteristics need to be borne in mind when extrapolating the current findings to other US or European populations.

The demographic characteristics of patients with GORD were similar to those revealed by other epidemiological data.<sup>17-19</sup> The age dependence of GORD in particular has been reported by many previous authors.<sup>8 20-26</sup> Patients with oesophageal ulcers and strictures are on average older than patients with oesophagitis only. In the past, this difference was interpreted to reflect the time it takes for the complications to develop from milder forms of reflux disease, but the present study did not reveal such progression. The age dependence of complicated oesophagitis could also stem from the decrease in the strength of defensive mechanisms with increasing age. Age leads to a decline in salivary secretion that helps to neutralise regurgitated acid covering the oesophageal lining.<sup>27</sup> Elderly patients with GORD were shown to have more severe reflux episodes and compromised clearance of acid

from their oesophagus as compared with younger patients.<sup>28</sup> These changes could stem from an age dependent loss in sphincter pressure and contractile strength.<sup>29</sup>

Most epidemiological data have shown that while reflux disease in general affects women more than men, severe forms of oesophagitis characterised by erosions, ulcers, and strictures tend to be more common in men.<sup>17-19</sup> The veterans population is predominantly comprised of men. Nevertheless, even in this population with a skewed sex distribution, the male preponderance for severe forms of GORD was obvious. As in other statistics, male preponderance was far less striking in pyrosis. The reasons for this peculiar behaviour of GORD are not well understood. Since acid secretion correlates with body surface area, men in general are characterised by higher amounts of acid output. Except for the striking example of Zollinger-Ellison syndrome, however, the association between the amount of acid output and the occurrence or severity of reflux disease has remained elusive.<sup>30-33</sup> It is conceivable that the sex specific variations reflect inborn differences in tissue resistance. It appears unlikely that they can be explained solely based on different exposure to the other known risk factors of GORD, such as obesity, smoking habits, and alcohol consumption in men as compared with women.<sup>25 34 35</sup>

The distribution of GORD by race remained an enigma for a long time. The discovery of *Helicobacter pylori* and the ethnic distribution of gastric infection by this bacterium has shed new light not only on peptic ulcer disease but also on GORD. Chronic inflammation of the gastric corpus mucosa secondary to infection with *H pylori* may reduce the number of functional gastric glands and acid secretion. In the long term, *H pylori* can lead to gastric atrophy and achlorhydria, thereby reducing the likelihood of GORD. While infection with *H pylori* promotes the development of peptic ulceration, it appears to decrease the occurrence of GORD at the same time. Labenz *et al* observed the development of erosive oesophagitis in 25.8% of duodenal ulcer patients within three years after *H pylori* had been eradicated by antibiotic therapy, as compared to 12.9% of subjects with persistent *H pylori* infection.<sup>36</sup> Non-whites could be protected against peptic oesophagitis and oesophageal adenocarcinoma of the gastric cardia by their higher prevalence rates of infectious gastritis with *H pylori*.<sup>37</sup> It is unknown whether differences in mucosal protection among various ethnic groups also contribute to the observed epidemiological pattern. The time trends of both peptic oesophagitis and adenocarcinoma of the cardia suggest that their prevalence is rising, as the overall prevalence of gastric infection with *H pylori* is declining.<sup>18 19 38</sup> This rise in the occurrence of GORD and oesophageal adenocarcinoma could stem from the concurrent decline in gastric infection by *H pylori*, especially in the white US population.

The similarity in the pathophysiology of different forms of GORD and their interdependence is clearly indicated by their clustering in

the same patient population. Patients with any given form of GORD were on average 10 times more likely to harbour another form of the disease than patients without GORD. The striking association between oesophageal ulcers and strictures supports the contention that strictures represent the end result of scarring. Oesophageal ulcers that penetrate deeper than mucosal erosions appear to be especially prone to heal with scars.

Our analysis did not reveal any clear cut temporal relationship between different forms of GORD. In the majority of instances, each of two forms of GORD were equally distributed among the three potential temporal relationships—that is, before, simultaneous, and after. Although testing the distributions by the  $\chi^2$  test revealed statistical significance in some associations, this appeared to be primarily a reflection of the large number of subjects available for comparison. There was a weak trend suggesting that mild forms may precede the more severe ones, while other distributions appeared to contradict such relationships. For instance, oesophagitis was diagnosed slightly more often before than after stricture, as opposed to oesophagitis being diagnosed more often after than before oesophageal ulcer. Overall, no particular pattern could be established consistently, and it seems that in patients diagnosed with any two forms of GORD, the initial presentation is determined by chance. Rather than progress through different grades, individual patients remain in the state reached initially or fluctuate between two close grades. Long term observations of patients with GORD point in the same direction.<sup>7-9 24 39</sup>

In conclusion, the studies of various populations with GORD have all revealed a remarkable similarity in the epidemiological patterns of the disease. Severe forms of GORD that are associated with complications tend to affect elderly, white, male subjects more often than their corresponding opposite demographic group. All forms of GORD cluster in the same patient population without showing a clear cut temporal sequence among different grades of disease severity. The extent of the breakdown in the normal physiology of the oesophagus might be responsible for the grade of GORD seen endoscopically. The lack of a temporal sequence between different grades of severity suggests that in most patients this breakdown reaches its full extent at the onset of the disease with little tendency to progress.

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