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ORIGINAL PAPER

Impact of generalized anxiety disorder (GAD) on prehospital delay of acute myocardial infarction patients. Findings from the multicenter MEDEA study

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Abstract

Background Anxiety has been identified as a cardiac risk factor. However, less is known about the impact of generalized anxiety disorder (GAD) on prehospital delay during an acute myocardial infarction (AMI). This study assessed the impact of GAD on prehospital delay and delay related cognition and behavior.

Methods Data were from the cross-sectional Munich examination of delay in patients experiencing acute myocardial infarction (MEDEA) study with a total of 619 ST-elevated myocardial infarction (STEMI) patients. Data on socio-demographic, clinical and psycho-behavioral characteristics were collected at bedside. The outcome was assessed with the Generalized Anxiety Disorder scale (GAD-7). A GAD-7 score greater than or equal to 10 indicates general anxiety disorder.

Results A total of 11.47% ($n = 71$) MI patients suffered from GAD. GAD was associated with decreased odds of delay compared to patients without GAD (OR 0.58, 95% CI 0.35–0.96), which was more significant in women (112 vs. 238 min, $p = 0.02$) than in men (150 vs. 198 min, $p = 0.38$). GAD was highly correlated with acute anxiety ($p = 0.004$) and fear of death ($p = 0.005$). Nevertheless, the effect remained significant after controlling for these two covariates. GAD patients were more likely to perceive a higher cardiovascular risk (OR 2.56, 95% CI 1.37–4.76) in 6 months before MI, which leads to the higher likelihood of making self-decision to go to the hospital (OR 2.68, 95% CI 1.48–4.85) in the acute phase. However, GAD was also highly associated with impaired psychological well-being, stress and fatigue ($p < 0.0001$).

Conclusions In AMI patients, GAD was independently associated with less prehospital delay, but led to an impaired psychological state.

Keywords Generalized anxiety disorder · Behavior response · Decision time · Prehospital delay

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Abbreviations

AMI	Acute myocardial infarction
STEMI	ST segment elevation myocardial infarction
PHD	Prehospital delay
MEDEA	Munich examination of delay in patients experiencing acute myocardial infarction
CHD	Coronary heart disease
MACE	Major adverse cardiac event

Introduction

Anxiety and fear are closely related basic emotions. They comprise anticipatory affective, cognitive, and behavioral changes executed to avoid or reduce the impact of a potential threat or a danger [1]. A key difference between fear and anxiety rests in the certainty or uncertainty of the threat. Fear is the response to a rather certain and objective threat, while anxiety is the response to a rather uncertain perceived subjective threat. Recent research has provided persuasive neurochemical and neuroanatomical evidence for this psychological distinction [2]. Once these anticipatory processes to uncertainty become maladaptive by being executed disproportionately to the likelihood or severity of the threat, pathological forms of anxiety develop, which can severely interfere with normal life [3, 4]. Anxiety disorders have been classified into several distinct disorders described in the DSM-5/ICD-10, one of which is referred to as generalized anxiety disorder (GAD) [5, 6]. With GAD, patients present with unfocused worry and anxiety that is not connected to recent stressful events. It is characterized by feelings of threat, restlessness, irritability, insomnia, tension, and physical symptoms such as palpitations, dry mouth, or sweating, lasting 6 month or longer. Due to the relapsing course of GAD, the disorder is often associated with seriously impaired social and occupational functioning. GAD is a common condition, with life time prevalence rates of 4–7% in the general population [7], women being twice as much affected [8]. In coronary heart disease (CHD) patients, its prevalence is even higher, ranging from 5.42 to 11.57% [9, 10].

Studies examining the impact of GAD on cardiovascular prognosis have yielded conflicting results: On one hand, GAD has been identified as an etiological risk factor of adverse cardiovascular events [11] such as ischemic stroke [12], myocardial infarction [9, 13]. On the other hand, recently several large scale studies show that GAD patients had a better prognosis following a cardiac event [14–17]. A probable reason for this positive effect of GAD might be due to higher alertness and increased health promoting behavior [15].

Time to treatment is a crucial determinant of survival in patients who have suffered an acute myocardial infarction (AMI) [18, 19]: the earlier interventional or thrombolytic therapy is given, the greater the reduction of infarct size and subsequent disability and mortality. Among numerous somatic and psychological factors which have the potential to influence delay time, it is already well-established that acute fear and anxiety during AMI onset reduce the decision delay to seek medical help [10, 11]. However, no study has been conducted so far to investigate the role of GAD on prehospital delay during AMI.

Thus, the objectives of our study are: (1) to assess the impact of GAD on prehospital delay and (2) to test whether a putative effect of GAD remains even after controlling for acute anxiety conditions, (3) to assess the impact of GAD on patient's behavioral responses to the symptoms during the acute phase of an AMI and (4) to further explore the impact of GAD on the post-acute course of AMI.

Methods

The multicenter, retrospective cross-sectional MEDEA study (Munich examination of delay in patients experiencing acute myocardial infarction) was conceived with the aim to evaluate prehospital delay of STEMI patients, and the factors which may contribute to prolonged delay.

Study design

The patients were recruited from eight different university or municipal hospitals with coronary care units, belonging to the Munich emergency system network clinics. The MEDEA study was approved by the Ethic Commission of the Faculty of Medicine of the Technische Universität München (TUM) on 10.12.2007 and the consent of the Munich Institut für klinische Forschung (IKF) for the participating four municipal hospitals (9.4.2008). The main inclusion criterion was diagnosis of STEMI as evidenced by typical clinical symptoms, ECG changes and myocardial biomarkers levels. Exclusion criteria were: In-hospital STEMI, resuscitation at AMI onset and language barriers or cognitive impairment impeding patients to answer the questionnaires properly. There were no age restrictions.

Standardized operation procedures (SOPs) were implemented to ensure the consecutive referral of eligible patients into the study. All patients were informed of the aim and procedures of the study and also that taking part in the study would have no effect on their treatment. All patients were required to sign a declaration of consent. Bedside interviews and self-administered questionnaires were conducted in the hospital ward within 24 h after referral from intensive care.

Sample

From 12 December 2007 until 31 May 2012, a total of 755 patients were screened for eligibility. In 619 patients, a diagnosis of STEMI was confirmed. Approximately, 18% of patients were excluded: 4% due to not meeting inclusion criteria and 14% due to absence of consent.

Data collection

The data collection process was divided into three sections. First, a structured bedside interview was conducted with trained personnel. Second, a self-administered questionnaire was filled by the patient without supervision. Third, data were collected from the hospitals' patient charts.

Measures

Prehospital delay (PHD)

Patients were asked to recall at what time acute symptoms began. The time difference between symptom onset and first ECG at hospital entry constitutes "prehospital delay" (PHD), measured in minutes. PHD was thus available as a continuous variable which was heavily left-skewed and did not approximate a normal distribution after log-transformations.

Generalized anxiety disorder

Anxiety was assessed with the German version of Generalized Anxiety Disorder scale (GAD-7). It is composed of 7 items, rated on a four-point Likert scale from not present to very high, leading to an overall score ranging from 0 to 21. A suspected diagnosis of GAD is defined by a GAD-7 score greater than or equal to 10. Using the threshold score of 10, the GAD-7 has a sensitivity of 82% for GAD [20].

Psychological measures

Depression was assessed with the Major Depression Inventory (MDI)—a self-report mood questionnaire able to generate an ICD-10 or DSM-IV diagnosis of clinical depression. The MDI contains 12 items. According to the DSM-IV definition, patients who had at least five symptoms in the MDI scale, of which at least one must be a 'core' symptom, were diagnosed with major depression [21].

Well-being was evaluated through the WHO-Five Well-Being index. It contains five items on a 6-point scale that range from 0 to 25. Thereafter, the raw scores are transformed into a scale that range from 0 to 100 [22].WHO-5 score less than or equal to 50 indicates suboptimal well-being [23]. Effectiveness of the index has been supported in evaluation of emotional well-being in patients with cardiovascular diseases.

Vital exhaustion was assessed using a four-item index on a five point Likert Scale that range from 0 to 16. Two items are from The Maastricht Questionnaire ("Do you often feel tired?" and "Do you often feel weak all over?"). The other two were obtained from the CES-D ("I felt that everything I did was an effort" and "I could not get going"). In present study, we applied the median split as a cut-off point, leading to an exhausted (>7) and non-exhausted (≤ 7) group. The predictive validity of the exhaustion index has been reported elsewhere as 3.18 and the internal consistency (Cronbach's) of this scale was 0.55 [24].

Psychological stress was assessed with three single-item questions relating to stress at work, at home and financial stress, rated on a four-point Likert scale, ranging from 3 (never) to 12 (permanent stress). Stress was defined as feeling irritable, filled with anxiety, or as having sleeping difficulties as a result of conditions at work or at home. In present study, we applied the median split as a cut-off point, leading to a stressed (>5) and non-stressed (≤ 5) group.

Patient behavioral responses to STEMI

A German version of the Response to Symptoms Questionnaire was applied [25], which assesses the behavior and subsequent reactions of both the patient as well as witnesses in the following areas: social context in which symptoms occurred and bystanders responses, behavioral responses to the symptoms, cognitive responses to the symptoms and emotional responses to the symptoms. The instrument also includes one item on symptom expectation, which measures the congruence between symptom expectation and perception (11 items, 5 point Likert scale, >3 rated was used as cut-off to define a high level).

Data analysis

Differences between dichotomous variables were assessed using the Chi square test. When comparing ordinal variables with more than two outcomes, the Mantel–Haenszel Chi square test was used. Differences in age were assessed using the *t* test. The nonparametric Wilcoxon test was used for assessing differences in median prehospital delay times. Multivariate Logistic regression model was applied to assess the association between GAD and patients' responses to the symptom onset. In addition, the additional effect of stress and exhaustion on patients' responses was also assessed by logistic regression model. Because anxiety level is highly correlated with other psychometric factors, logistic regression with different grades of adjustments for psychological factors was applied to assess the association between GAD and the chance of longer delay. Patients who delayed more than two hours are defined as delayed group. Adjustments were made for fear of death, acute anxiety during the symptom onset (model 2), and additionally for stress (model 3), exhaustion (model 4) and depression (model 5).The relative risk for longer delay is presented as odds ratio (OR) with 95% confidence interval (95% CI).

All statistical analyses were run in SAS (Version 9.3, SAS-Institute Inc., Cary, NC, USA). The significance level was set at $p<0.05$. The analysis and description in this paper follow the STROBE guidelines for cross-sectional studies [26].

Results

A total of 619 patients were included in the present study with 162 (26.17%) women and 457 (73.83%) men aged between 30 and 93 years (mean age 62.50 years, SD 12.15). In the total sample, the median delay time was 200 (100–652) minutes.

Prevalence and distribution of GAD in patients with STEMI

The GAD-7 score was right-skewed with a mean of 5.98 ± 4.40 and a median of 5, leading to a total of 71 (11%) patients with GAD (GAD-7 ≥ 10). We identified a similar prevalence in women (11.11%) and in men (11.60%) ($p = 0.87$). As shown in Table 1, patients with GAD were more likely to be younger ($p = 0.05$), but did not show differences with respect to social demographic characteristics (education levels, employment status and living situation).

Characteristics of patients with GAD during the 6 months prior to STEMI

As displayed in Table 1, patients with GAD were more likely to report stress ($p < 0.0001$), vital exhaustion ($p < 0.0001$), suboptimal well-being ($p < 0.0001$) and depression ($p < 0.0001$).

Impact of GAD on patients' symptom perception, behavior responses during STEMI

In the acute phase of STEMI, patients with GAD were more likely to perceive exhaustion ($p = 0.04$), fear of death ($p = 0.0005$) and a higher level of acute anxiety ($p = 0.004$). As can be seen in Table 2, patients with GAD perceived a higher subjective cardiovascular risk as compared to patients without GAD (OR 0.39, 95% CI 0.21–0.73) and were more likely to make self-decisions to go to the hospital (OR 2.68, 95% CI 1.48–4.85). The associations remained significant in GAD patients who additionally suffered from stress or vital exhaustion.

Impact of GAD on prehospital delay

The median delay time in patients with GAD tended to be shorter than in patients without GAD (median delay time 134 vs. 213 min, $p = 0.059$).

GAD was associated with decreased odds of delay (delay time > or ≤ 2 h) compared to patients without GAD (OR 0.58, 95% CI 0.35–0.96). As can be seen in Table 3, the effects were independent from the acute anxiety at onset of symptoms and even fear of death (model 2) and remained significant after stepwise adjustment for stress, exhaustion and depression (model 3–5).

As can be seen in Fig. 1, sex stratified analysis illustrated that the effect of GAD on prehospital delay in women (112 vs. 238 min, $p = 0.02$) is more significant than in men (150 vs. 198 min, $p = 0.38$). Likewise, GAD was associated with decreased odds of delay longer than 2 h in women (OR 0.30, 95% CI 0.11–0.85, $p = 0.02$) but not in men (OR 0.71, 95% CI 0.40–1.30, $p = 0.26$).

Table 1 Socio-demographic and clinical characteristics of the study population stratified by with GAD ($n = 71$) and without GAD ($n = 548$)

	GAD ($n = 619$)			*p* value
	Missing	With GAD	Without GAD	Overall
All patients	–	71 (11.47%)	548 (88.53%)	
Socio-demographic factors				
Age (> 65)	–	58.71 ± 11.91	62.98 ± 12.86	0.005
Sex (female)		18 (11.11%)	144 (88.89%)	0.87
Sex (male)	–	53 (11.60%)	404 (88.40%)	
Living alone	–	27 (38.03%)	155 (28.28%)	0.09
Employed	–	37 (52.11%)	267 (48.72%)	0.59
Education (secondary school and above)	–	25 (35.21%)	231 (42.15%)	0.26
AMI symptoms				
Chest pain		63 (88.73%)	489 (89.23%)	0.90
Dyspnea		29 (40.85%)	165 (30.16%)	0.07
Racing heart		10 (14.08%)	44 (8.03%)	0.22
Sweating		48 (67.61%)	305 (55.76%)	0.06
Faint		5 (7.04%)	30 (5.48%)	0.59
Exhaustion		16 (22.54%)	74 (13.53%)	0.04
Vomiting		11 (15.49%)	78 (14.26%)	0.78
Nausea		29 (40.85%)	212 (38.76%)	0.73
Heart burn		6 (8.45%)	32 (5.85%)	0.39
Stomach ache		9 (12.68%)	37 (6.76%)	0.07
Psychological factors				
Perceived stress		56 (24.89%)	10 (3.47)	< 0.0001
Vital exhaustion		53 (23.66%)	18 (4.56)	< 0.0001
Fear of death		20 (28.99%)	68 (13.00%)	0.0005
Acute anxiety		31 (43.66%)	148(27.21%)	0.004
Depression		25 (35.21%)	13(2.82%)	< 0.0001
Optimal well-being		21 (29.58%)	367 (66.97%)	< 0.0001

Values are *n* (%). *p* values were considered significant when $p < 0.05$

Table 2 The impact of GAD, further stratified for GAD population with stress ($n=56$) and exhaustion ($n=53$)

	GAD vs. no GAD (71 vs. 548) OR (95% CI)	GAD with stress vs. others (56 vs. 457) OR (95% CI)	GAD with exhaustion vs. others (53 vs. 566) OR (95% CI)
Cognitive responses			
Heart misattribution	1.00 (0.61–1.65)	1.01 (0.58–1.75)	0.97 (0.55–1.71)
Failed to recognize the symptoms as MI	1.32 (0.81–2.17)	1.51 (0.87–2.63)	1.47 (0.83–2.59)
Insufficient risk perception	**0.39 (0.21–0.73)**	**0.32 (0.16–0.61)**	**0.36 (0.18–0.72)**
Behavioral responses			
Take medicine	0.86 (0.52–1.44)	1.06 (0.52–2.17)	1.29 (0.59–2.81)
Wait until the symptom resolves	0.70 (0.43–1.16)	0.69 (0.39–1.19)	0.90 (0.50–1.61)
Continue doing the ongoing activity	1.01 (0.54–1.88)	1.03 (0.52–2.06)	1.06 (0.52–2.18)
Try to relax	1.25 (0.75–2.10)	1.05 (0.60–1.85)	1.45 (0.79–2.63)
Call someone for help	2.32 (0.55–9.88)	1.80 (0.42–7.68)	1.65 (0.39–7.07)
Call general physician	0.95 (0.41–2.17)	1.41 (0.49–4.05)	1.29 (0.45–3.72)
Call emergency doctor	1.24 (0.75–2.05)	1.21 (0.69–2.12)	1.52 (0.86–2.69)
Used ambulance to get to the hospital	0.86 (0.52–1.44)	0.90 (0.51–1.59)	0.76 (0.42–1.38)
Drive themselves to the hospital	1.28 (0.68–2.41)	1.16 (0.58–2.31)	1.63 (0.75–3.55)
Made self-decision to go to the hospital	**2.68 (1.48–4.85)**	**2.89 (1.46–5.70)**	**2.67 (1.35–5.29)**
Post-acute course			
With complication	**0.44 (0.20–0.99)**	0.60 (0.26–1.35)	0.43 (0.17–1.10)*
Cardiac arrest	2.11 (0.76–5.84)	**2.81 (1.01–7.83)**	0.97 (0.00–4.24)
Intensive care ≥ 3 days	0.91 (0.54–1.52)	0.95 (0.53–1.68)	0.89 (0.50–1.59)

Bold means significant p values at <0.05 level

*$p=0.08$

Table 3 Association of GAD and prehospital delay assessed by logistic regression, adjusted by fear of death, acute anxiety, stress, exhaustion and depression

Emotional factors	Delay > 2 h vs. delay ≤ 2 h (426 vs. 193) OR (95% CI)				
	Model 1	Model 2	Model 3	Model 4	Model 5
GAD	**0.58 (0.35–0.96)**	**0.60 (0.35–0.99)**	**0.48 (0.27–0.84)**	**0.49 (0.27–0.89)**	**0.50 (0.26–0.97)**
Fear of death		0.64 (0.33–1.24)	0.77 (0.35–1.67)	0.77 (0.35–1.67)	0.78 (0.36–1.71)
Acute anxiety		0.96 (0.91–1.01)	0.96 (0.90–1.02)	0.96 (0.90–1.02)	0.96 (0.90–1.01)
Stress			1.05 (0.94–1.18)	1.05 (0.94–1.18)	1.04 (0.93–1.12)
Exhaustion				1.01 (0.67–1.52)	0.98 (0.67–1.50)
Depression					1.00 (0.44–2.26)

Bold means significant p values at <0.05 level

All the models were adjusted for sex and age

Model 1: the crude model

Model 2: adjusted with acute anxiety condition (including fear of death and acute anxiety)

Model 3: further adjusted with self-perceived burden of daily stress

Model 4: further adjusted with vital exhaustion

Model 5: further adjusted with depression

The post-acute course of patients with GAD

In the post-acute infarction phase during ICU stay, patients with GAD were less likely to have complications (OR 0.44, 95% CI 0.22–0.99). The GAD patients additionally suffering from stress were more likely to experience in-hospital cardiac arrest, but did not show differences regarding complication and ICU stay compared to their counterparts. GAD

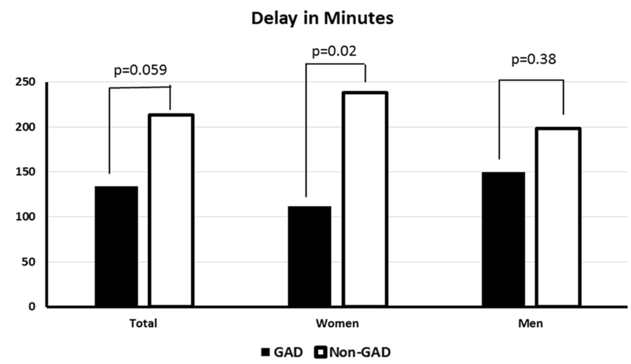

Fig. 1 Nonparametric test for comparing median delay time (in min) for all patients with and without GAD and stratified for women and men

patients suffering additionally from vital exhaustion tended to experience less cardiac complications (OR 0.43, 95% CI 0.17–1.10).

Discussion

To the best of our knowledge, this is the first comprehensive evaluation of the impact of GAD on prehospital delay in patients facing an AMI. The major finding of the present study is that GAD had a favorable effect on reducing prehospital delay during AMI. This effect of GAD on prehospital delay was significant in women, while in men, we identified solely a non-significant trend. Moreover, GAD was associated with better prognosis in the post-acute phase of AMI.

Patients suffered from GAD also presented a comorbidity pattern of impaired mental health, meaning the patients with GAD were also significantly more likely to suffer from acute anxiety, depression, vital exhaustion and perceived stress. It has been well-documented that pronounced acute anxiety/fear owing to the sudden onset of the life-threatening AMI leads to a shorter delay time, hereby favoring a good prognosis [27–29].

Of note, the beneficial effects of GAD on prehospital delay and prognosis found in our homogeneous STEMI sample remained significant even after we controlled for acute fear of death [30], depression, exhaustion and perceived stress. This finding underscores that GAD is a powerful and independent protective factor on its own in patients facing an AMI.

This is a remarkable finding, which points to a specific alertness of GAD patients more likely to be present at the time long before the onset of AMI. This assumption is supported by our finding showing that GAD patients had a higher self-perceived MI risk than non-GAD patients. In that line, GAD has been found to be a 'driver' for individuals to address their health needs more regularly and conscientiously and seek help at the early signs of the disease. Dubayova et al. [31] reported in a systemic review including 15 studies that being 'anxious' has a significant positive effect on decision making in help-seeking behavior. Parker et al. [14] found that GAD patients received more medical tests and tended to take part more often in post-AMI rehabilitation programs. Interestingly, GAD patients did not experience a different pattern of acute symptoms compared to non-GAD patients. This is noteworthy because it is unlikely that the GAD patients sought help faster because of more severe symptoms.

Moreover, the study reveals the association of GAD patients with a better prognosis in the post-acute phase of AMI. It is not unlikely that this is a consequence of the reduced delay time in GAD patients as well, based on the earlier treatment and hereby improved course with less symptoms, since every minute of delay to treatment for STEMI has previously been shown to affect the 1-year mortality [32]. Yet, the post-acute outcome was not favorable anymore, if GAD was accompanied by stress or exhaustion (Table 2).

Contrary to expectation, we found no sex difference of GAD prevalence in our clinical sample. This is remarkable because in general population, women are twice as much affected with GAD than men [8]. The analysis shows a sex-specific impact of anxiety on delay time though. In women, the difference of delay time was highly significant, whereas in men, there was only a trend towards a reduced delay. Currently, we have no possible reasons to explain the differences.

Although this study identified favorable effects in patients meeting GAD criteria having shorter time to treatment and fewer complications, it seems to be essential to balance this 'advantage' with the disease burden of GAD itself: GAD patients were more likely to suffer from higher levels of negative emotions (including depression, exhaustion and perceived stress and thus impaired psychological well-being). This is in line with the observation showing that anxiety and depression frequently co-occur [33, 34].

To our knowledge, this is the first study investigating the impact of generalized anxiety disorder on prehospital delay in a strictly defined population of STEMI patients. There are a few study limitations that are worth considering. First, all data were collected at bedside within a very narrow time frame (< 24 h after referral from intensive care) after STEMI, nevertheless, we cannot fully exclude the possibility of recall bias. We had relatively small numbers of women, so replications of these results in larger datasets are warranted. Furthermore, selection bias could have resulted from excluding STEMI patients who died before reaching the hospital. Finally, GAD diagnosis was based on GAD-7 questionnaire data which provides a sensitivity of 82% for GAD [35] using a threshold score of 10.

Conclusion

Our study demonstrates that in patients facing an AMI, GAD is associated with an increased chance of early arrival and thus had fewer complications, despite its known adverse effects on psychological well-being. The higher perceived MI risk and the higher chance of making self-decision to seek medical help in GAD patients suggests that GAD patients are particularly sensitive to early sign of the disease, ultimately resulting in shorter time to treatment and better prognosis. The shorter delay time and appropriate behavioral responses during AMI indicated the protective effect of GAD on patients' acute situation. However, our study does not provide information regarding long-term effect of GAD on patients' cardiac outcome. Further investigation is necessary to reveal whether the impaired psychological well-being caused by GAD will be detrimental for long term prognosis. This will provide necessary clinical implication for the appropriate timing to intervene GAD in CHD patients.

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Compliance with ethical standards

Conflict of interest None to declare.

Ethic statements All patients were informed of the aim and procedures of the study and also that taking part in the study would have no effect on their treatment. All patients were required to sign a declaration of consent. Details that might disclose the identity of the subjects under study has been omitted.

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