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RESEARCH ARTICLE

ADHERENCE TO ANTIEPILEPTIC DRUGS AMONG EPILEPTIC PATIENTS IN TAIF: PREVALENCE AND DETERMINANTS

Naif Edah Alomairi
Department of Internal Medicine, College of Medicine, Taif University, Taif 21944, Saudi Arabia, Neurology Consultant, Alhada Armed Forces Hospital, Taif, Saudi Arabia.

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Abstract

Background: Inadequate adherence to antiepileptic drugs (AEDs) leads to increased mortality and morbidity due to poor seizure control. This has direct and indirect effects on healthcare system costs, including disease progression, prolonged hospitalization, and premature disability.

Objectives: To investigate therate and determinants of non-adherence to AEDs.

Patients and Methods: A hospital-based cross-sectional study was conducted at Al-Hada Armed Forces Hospital in Taif City. The study involved adult epileptic patients who visited the neurology outpatient clinic of the hospital between June 1st and August 31st, 2024. Data was gathered through patient interviews using a validated Arabic questionnaire and a review of medical charts. Adherence to anti-epileptic medications over the past 2 weeks was self-reported by the patients using a 4-item Morisky Green Levine Medication Adherence Scale (MGLS).

Results: A total of 318 epileptic patients were included in the study. The age of more than a third of the patients (35.3%) ranged between 18 and 30 years. High adherence to AEDs was observed among the majority of patients (81.1%), while low adherence was reported in 9.7% of them. The results of multivariate logistic regression showed that patients aged between 41 and 50 years were at almost a three-fold higher risk of being low/intermediate adherent to AEDs compared to those aged 18-30 years (aOR=2.96; 95% CI: 1.22-7.15, p=0.016).Patients who have experienced 1-3 seizures per year and those with a frequency of ≤1 seizure per month were found to have a significantly higher likelihood of showing low or intermediate adherence to AEDs compared to patients who have been seizure-free for more than 2 years (aOR=2.87; 95% CI: 1.15-7.20, p=0.025 and aOR=3.42; 95% CI: 1.60-7.28, p = 0.001, respectively).Compared to patients who did not experience any adverse reactions to AEDs, those who did were at a higher risk of being low/intermediate adherent to AEDs (aOR=5.13; 95% CI: 1.62-16.21, p=0.005).

Conclusion: The adherence to anti-epileptic drugs (AEDs) among epileptic patients was generally high. However, a significant proportion of patients reported low to intermediate adherence. Therefore,

Corresponding Author:- Naif Edah Alomairi
Address:- Department of Internal Medicine, College of Medicine, Taif University, Taif 21944, Saudi Arabia, Neurology Consultant, Alhada Armed Forces Hospital, Taif, Saudi Arabia.

healthcare providers should encourage adherence to AEDs, paying special attention to checking for any potential adverse effects.

Introduction:-

Epilepsy is a neurologic disorder characterized by frequent convulsions, and approximately 50 million patients are affected by the disease all over the world; mainly in developing countries [1-3]

According to the World Health Organization (WHO), adherence is the extent to which a person's behavior, including taking medication, following a prescribed diet, and/or making lifestyle changes, aligns with the recommendations of the healthcare provider.[4] Inadequate adherence to anti-epileptic drugs (AEDs) leads to increased mortality and morbidity as a result of poor seizure control, which has both direct and indirect impacton the healthcare system cost as a result of disease progression, prolonged hospitalization and pre-mature disability[5].Additionally, non-adherence to AEDs It is important to remember that not taking antiepileptic drugs (AEDs) as prescribed can lead to higher rates of death and disease due to inadequate seizure control. This can, directly and indirectly, impact healthcare costs through the progression of the disease; longer hospital stays, and premature disability. Additionally, non-adherence to AEDs significantly impairs the quality of life for affected patients.[6]

The overall adherence to antiepileptic medications is poor, particularly in developing countries. This is mainly due to a lack of knowledge about antiepileptic medications, the frequency and duration of seizures, side effects of medications, the complexity of polytherapy treatment, and uncontrolled seizures. Additionally, non-adherence to AEDs is significantly affected by the high cost and lack of availability of drugs, low education, being female, and cultural beliefs.

The majority of patients with epilepsy in developing countries are not adherent to AEDs, which seriously affects the control of seizures and results in severe morbidity and mortality. To the best of our knowledge, this issue has not been investigated in the Kingdom of Saudi Arabia. Therefore, it is important to define the extent and factors contributing to non-adherence to AEDs in our culture using a validated tool.

Patients and Methods:-

A hospital-based cross-sectional study was conducted in Taif City, which is located in Makkah Province, Western Region of Saudi Arabia. Taif City, with an estimated population of (717,334) (based on the 2024 census), is home to several tertiary care hospitals, including the Al-Hada Armed Forces Hospital, where the study was conducted at the neurology outpatient clinics.

Adult patients with epilepsy who visited the neurology outpatient clinic at Al-Hada Armed Forces Hospital in Taif City between June 1st and August 31st, 2024, were eligible for the study,provided they met the inclusion criteria. Diagnosis of epilepsy was based on a detailed medical history and neurological evaluation by a neurologist, including the use of electroencephalography and neuroimaging techniques such as computed tomography scan (CT) and magnetic resonance imaging (MRI).

Patients included in the study were required to have been on antiepileptic drugs for a minimum of 6 months, be adults aged 18 years and older, and belong to all nationalities. Individuals with mental disorders were excluded from the study.

The minimum required sample size (n) was estimated using the formula n = z2pq/d2, where z is the value from the standard normal distribution reflecting the confidence level that was used (Z = 1.96 for 95%), d is the desired margin of error (0.05), p is the proportion of non-adherence in the population. (p=0.292 i.e.29.2% was used) according to a recent study carried out in UAE,[13] and q=1-p (0.708). Accordingly, the estimated minimum required sample size was 318 patients; however, an additional 10% will be included to compensate for none or incomplete participants` responses to the study questionnaire.A convenience sampling technique was adopted to select consecutive eligible patients from neurology outpatient clinics, Alhada Armed Forces Hospital, Taif and inviting them to complete the study questionnaire that was followed till the required sample size had been achieved.

Data were collected through both interviewing of patients using an Arabic-validated questionnaire and a medical charts review that consists of three main parts. The first part covers the socio-demographic characteristics of the patients.Comprising age, gender, nationality, place of residency, marital status, educational level, and employment status. The second part deals with theMedical and epilepsy-related history, including duration of epilepsy, type of epilepsy, type of AED therapy, type of AED used, seizure frequency, adverse drug reactions, and history of co-morbid chronic disease. The third partincludes self-reportingof adherence to anti-epileptic medications over the last 2 weeks using the Morisky Green Levine Medication Adherence Scale(MGLS), which consists of 4 questions with "yes: and "no" responses. Yes response was assigned a score of "1",whereas no response was assigned a score of "0". Thus, the total score for each patient will range from 0 to 4. The lower the score, the more adherence. A total score of 0 indicated high adherence; a score of 1- 2 indicated intermediate adherence; and a score of 3- 4 indicated low adherence.[14, 15]

Polytherapy was used to define the daily consumption of 5 or more medications, and co-morbidity was used to describe patients diagnosed with two or more diseases.[16]

The data entry and analysis were conducted using the Statistical Package of the Social Sciences (SPSS) program for Windows version 28, developed by IBM Corporation in Armonk, NY, USA. The study employed frequency and percentage to describe categorical variables. To test the association between categorical variables, the chi-square test and Fischer exact test were used. Additionally, the study employed a multivariate logistic regression model to identify determinants for non-adherence while counting and controlling for confounding factors.

Throughout the study, a P-value of less than 0.05 was considered to be statistically significant.

The study proposal received approval from Al-Hada Armed Forces Hospital Institutional Review Board (IRB) Committee under (the reference number H-02-T-078, Record 902, dated 27th May 2024.)

Results:-

A total of 318 epileptic patients were included in the study. Table 1 provides a summary of their socio-demographic characteristics. The age of over a third of the patients (35.3%) ranged between 18 and 30 years, while 5% were over 60 years old. Females accounted for 57.2% of the patients, and the vast majority (99.4%) were Saudi nationals. The majority of the patients (88.1%) lived in urban areas, and 66.4% were married. More than a third (35.6%) had completed university or postgraduate education, and 81.8% were not employed.

The majority of patients (61%) had been experiencing epilepsy for over 10 years. The most commonly reported type of epileptic seizure was general tonic-colonic (78.3%), and nearly half of the patients (48.7%) had been seizure-free for more than two years. About half of the patients (50.6%) were on multiple antiepileptic drugs, and 48.1% were taking a combination of new and old medications. Adverse reactions to antiepileptic drugs were reported by 5.3% of patients, while 7.9% had a history of comorbidity **(**Table 2**.)**Although most patients (81.1%) showed high adherence to their antiepileptic medications, 9.7% reported low adherence.Figure 2. The study found that the highest rate of high adherence to AEDs (anti-epileptic drugs) was seen in patients over 60 years old (93.7%), while the lowest rate was observed in patients aged 51 to 60 years (70%), with a significance of p=0.017. A majority of Saudi patients (81.6%) showed high AED adherence compared to non-Saudis, with a significance of p=0.035. Additionally, all patients with primary school education and the majority (85%) with university or higher education demonstrated high adherence to AEDs, whereas only 66.7% of illiterate patients showed high adherence, with a significance of p=0.008. The study did not find any associations between patients' gender, marital status, place of residence, or job status and their level of adherence to AEDs. These findings are summarized in Table 3. The majority of patients who were either seizure-free for ≤2 years, 92%, or for >2 years, 89%,expressed a high level of adherence to their anti-epileptic drugs (AEDs). This is in contrast to only 69.1% of patients with a higher frequency of seizures (≤1 per month). Patients who were on new AEDs showed the highest level of adherence at 88.8%. Those who reported experiencing adverse drug reactions were less likely to adhere to their AEDs, with only 47.1% showing high adherence compared to 82.3% among those who did not report adverse reactions. Factors such as duration of epilepsy, type of epileptic fits, type of epileptic therapy, and history of co-morbidity did not show a significant association with the level of adherence to AEDs. These findings are summarized in Table 4.In the results of the multivariate logistic regression analysis presented in Table 5, it was found that patients between the ages of 41 and 50 had a nearly threefold greater risk of being low to intermediate adherent to AEDs compared to those aged 18-30 years (aOR=2.96; 95% CI: 1.22-7.15, p=0.016). Compared to patients who have been seizure-free for more than 2

years, those who experience seizures with a higher frequency (1-3 times per year and less than or equal to 1 time per month) are significantly more likely to show low or intermediate adherence to AEDs (adjusted odds ratio (aOR)=2.87; 95% CI: 1.15-7.20, p=0.025 and aOR=3.42; 95% CI: 1.60-7.28, p=0.001, respectively).Compared to patients who did notreport any adverse reactions to AEDs, those who did reportadverse reactions to these drugs were at ahigher risk for being low/intermediate adherent to AEDs (aOR=5.13; 95% CI: 1.62-16.21, p=0.005). Patient`s nationality, education and type of anti-epileptic drug were not significantly associated with a level of adherence to AEDs after accounting for confounders.

Discussion:-

The present study revealed that 81.1% of epileptic patients showed high adherence to AEDs. This figure is similar to those reported in two other studies conducted in the United Arab Emirates (70.8%) and the United States (74%). However, it is higher than those reported in similar studies carried out in India and Jordan, which found that almost half of the epileptic patients were non-adherent to the AEDs. In a study conducted in the Sudan (2019), the rate of non-adherence was 35%.In Ethiopia (2022), non-adherence to antiepileptic drugs (AEDs) was observed in 40.3% of patients. A recently published systematic review and meta-analysis that included 9 cross-sectional studies with 1772 patients conducted in India found that the pooled prevalence of adherence to AEDs was 49.9%. Another recent systematic review and meta-analysis carried out in Ethiopia included 12 studies with a total of 3,416 epileptic patients; the pooled prevalence of non-adherence to antiepileptic drugs was 42%.Ibinda et al. (2017) conducted a cross-sectional survey to investigate non-adherence to AEDs among 1,303 epileptic patients across African countries. They reported that the overall prevalence of non-adherence to AEDs was 63.1% as measured by detectable AED levels, and self-reported non-adherence was 65.1%. This study sheds light on the high rates of non-adherence to AEDs among epileptic patients in African countries.In a study conducted in Singapore in 2017, it was found that 72.3% of patients showed high adherence to their prescribed medication, while 27.7% had low adherence. The differences in adherence rates across various studies, including the current one, may be attributed to variations in patient characteristics and the methods used to measure medication adherence to antiepileptic drugs (AEDs).In this study, adherence to AEDs has been associated with patients' age, frequency of seizures and development of adverse drug reactions. Other factors reported in similar studies include taking multiple medications, duration of epilepsy, lower education level, comorbidity, female sex, history of hospitalization and substance use.[6, 18, 19, 26]

Determinants linked with low to intermediate adherence to AEDs in this study included the patients between the ages of 41 and 50, those experiencing more frequent seizures (1-3 per year or ≤1 per month), and those having adverse reactions to these medications. It's significant to note that different studies conducted internationally yielded varying results.In a study conducted in India (2024), determinants associated with non-adherence to AEDs were lower socioeconomic status, lower education levels, being on multiple medications, experiencing side effects from the medication, and substance abuse.[22]In a study conducted in Ethiopia in 2022, multivariate logistic regression analysis revealed that patients who experienced medication side effects, those taking multiple medications, and patients with co-morbidities were more likely to report medication non-adherence. In a similar study in 2021, the determinants for non-adherence were found to be paying for medications, taking medications for more than a year, having co-morbidities, and feeling stigmatized.In a study conducted in the United Arab Emirates in 2020, it was found that lower education level and experiencing a seizure within the last 6 months were significant factors contributing to non-adherence to medication. On the other hand, taking levetiracetam was associated with a decreased risk of non-adherence. In another study in Sudan in 2019, it was found that attitude towards anti-epileptic drugs (AEDs) and the presence of side effects from AEDs were significantly associated with adherence. In a cross-sectional survey conducted by Ibinda et al. (2017) among epileptic patients in various African countries, it was found that non-adherence to treatment was more prevalent among children than adults. For children, factors such as lack of previous hospitalization and learning difficulties were independently associated with non-adherence. Among adults, the independent factors associated with non-adherence to antiepileptic drugs (AEDs) included the history of home delivery, absence of burn marks, and not seeking traditional medicine. In a study conducted in Singapore in 2017, it was found that socioeconomic status and the type of epilepsy were important factors related to adherence to medication. There was a likelihood that patients withepilepsy and those from the middle/lower-middle socioeconomic classesadhered to their medication. Additionally, variations in factors associated with low adherence to antiepileptic drugs (AEDs) could be due to cultural differences and the diverse sociodemographic characteristics of patients.

One of the limitations of the current study is that it was conducted in only one hospital, which could impact the ability to generalize its findings to all other hospitals. Additionally, as it is a cross-sectional study, it cannot establish

a causal effect relationship. However, despite these limitations, the study addressed an important topic that is rarely investigated in Saudi Arabia, and its findings could be important for clinical practice.

Table 1:- Socio-demographic characteristics of the patients (n=318).

Variables	Frequency	Percentage
Age in years		
18-30	112	35.3
31-40	82	25.8
41-50	58	18.2
51-60	50	15.7
>60	16	5,0
Gender		
Male	136	42.8
Female	182	57.2
Nationality		
Saudi	316	99.4
Non-Saudi	2	0.6
Place of residency		
Urban	280	88.1
Rural	38	11.9
Marital status		
Single	90	28.3
Married	211	66.4
Divorced	17	5.3
Educational level		
Illiterate	57	17.9
Primary	20	6.3
Intermediate	37	11.6
Secondary	91	28.6
University/postgraduate	113	35.6
Employment status		
Not working	260	81.8
Working	58	18.2

Table 2:- Medical characteristics of the patients (n=318).

Variables	Frequency	Percentage
Duration of epilepsy in years		
<5	53	16.7
5-10	71	22.3
>10	194	61.0
Type of epileptic fits		
General tonic colonic	249	78.3
Focal	62	19.5
Absence seizure	7	2.2
Type of epileptic therapy		
Monotherapy	157	49.4
Polytherapy	161	50.6
Frequency of epileptic fits		
≤1 per month	97	30.5
1-3 per year	41	12.9
Seizure- free for ≤2 years	25	7.9
Seizure -free for >2 years	155	48.7
Type of antiepileptic drug		
New	89	28.0
Old	76	23.9
Combination	153	48.1

Adverse antiepileptic drugs` reaction		
No	231	72.7
Yes	17	5.3
Don`t remember	70	22.0
History of comorbidity		
No	293	92.1
Yes	25	7.9

Table 3:- Socio-demographic factors associated with adherence to anti-epileptic drugs among patients with epilepsy: Univariate analysis.

Independent variables	**Adherence to AEDs**		**p-value***
	Low/intermediate N=60 N (%)	**High N=258 N (%)**	
Age in years			
18-30 (n=112)	21 (18.8)	91 (81.3)	
31-40 (n=82)	8 (9.8)	74 (90.2)	
41-50 (n=58)	15 (25.9)	43 (74.1)	
51-60 (n=50)	15 (30.0)	35 (70.0)	
>60 (n=16)	1 (6.3)	15 (93.7)	0.017
Gender			
Male (n=136)	23 (16.9)	113 (83.1)	
Female (n=182)	37 (20.3)	145 (79.7)	0.441*
Nationality			
Saudi (n=316)	58 (18.4)	258 (81.6)	
Non-Saudi (n=2)	2 (100)	0 (0.0)	0.035**
Place of residency			
Urban (n=280)	56 (20.0)	224 (80.0)	
Rural (n=38)	4 (10.5)	34 (89.5)	0.115**
Marital status			
Single (n=90)	10 (11.1)	80 (88.9)	
Married (n=211)	47 (22.3)	164 (77.7)	
Divorced (n=17)	3 (17.6)	14 (82.4)	0.076*
Educational level			
Illiterate (n=57)	19 (33.3)	38 (66.7)	
Primary (n=20)	0 (0.0)	20 (100)	
Intermediate (n=37)	6 (16.2)	31 (83.8)	
Secondary (n=91)	18 (19.8)	73 (80.2)	
University/postgraduate (n=113)	17 (15.0)	96 (85.0)	
			0.008*
Employment status			
Not working (n=260)	49 (18.8)	211 (81.2)	
Working (n=58)	11 (19.0)	47 (81.0)	0.983*

AEDs: Anti-epileptic drugs **OR: Odds ratio**
***Chi-square test** **CI: Confidence interval**
****Fischer Exact test**

Table 4:- Medicalfactors associated with adherence to anti-epileptic drugs among patients with epilepsy: Univariate analysis.

Independent variables	**Adherence to AEDs**		**p-value***
	Low/intermediate N=60 N (%)	**High N=258 N (%)**	
Duration of epilepsy in years			
<5 (n=53)			
5-10 (n=71)	8 (15.1)	45 84.9)	

>10 (n=194)	15 (21.1)	56 (78.9)	
	37 (19.1)	157 (80.9)	0.692
Type of epileptic fits			
General tonic colonic (n=249)	49 (19.7)	200 (80.3)	
Focal (n=62)	9 (14.5)	53 (85.5)	
Absence seizure (n=7)	2 (28.6)	5 (71.4)	0.521
Type of epileptic therapy			
Monotherapy (n=157)	25 (15.9)	132 (84.1)	
Polytherapy (n=161)	35 (21.7)	126 (78.3)	0.185
Frequency of epileptic fits			
≤1 per month (n=97)	30 (30.9)	67 (69.1)	
1-3 per year (n=41)	11 (26.8)	30 (73.2)	
Seizure-free for ≤2 years (n=25)	2 (8.0)	23 (92.0)	
Seizure -free for >2 years (n=155)	17 (11.0)	138 (89.0)	
			<0.001
Type of antiepileptic drug			
New (n=89)	10 (11.2)	79 (88.8)	
Old (n=76)	13 (17.1)	63 (82.9)	
Combination (n=153)	37 (24.2)	116 (75.8)	0.041
Adverse antiepileptic drugs` reaction			
No (n=231)			
Yes (n=17)	41 (17.7)	190 (82.3)	
Don`t remember (n=70)	9 (52.9)	8 (47.1)	
	10 (14.3)	60 (85.7)	0.001
History of comorbidity			
No (n=293)	55 (18.8)	238 (81.2)	
Yes (n=25)	5 (20.0)	20 (80.0)	0.880*

AEDs: Anti-epileptic drugs **OR: Odds ratio**
***Chi-square test** **CI: Confidence interval**
****Fischer Exact test**

Table 5:- Predictors of low/intermediate adherence to anti-epileptic drugs among patients with epilepsy: Results of multivariate logistic regression analysis.

	aOR	**95% CI**	**p-value**
Age in years			
18-30[a]	1.0	---	---
31-40	0.54	0.20-1.42	0.211
41-50	2.96	1.22-7.15	0.016
51-60	2.33	0.95-5.71	0.066
>60	0.45	0.05-3.93	0.472
Frequency of epileptic fits			
Seizure free for >2 years	1.0	---	---
Seizure free for ≤2 years	0.69	0.14-3.37	0.648
1-3 per year	2.87	1.15-7.20	0.025
≤1 per month	3.42	1.60-7.28	0.001
Adverse antiepileptic drugs` reaction			
No[a]			
Yes	1.0	---	---
Don`t remember	5.13	1.62-16.21	0.005
	0.91	0.40-2.07	0.819

[a]: Reference category
aOR: Adjusted odds ratio
CI: Confidence interval
Terms of patient`s nationality, education and type of anti-epileptic drug were removed from the final logistic regression model (not significant)

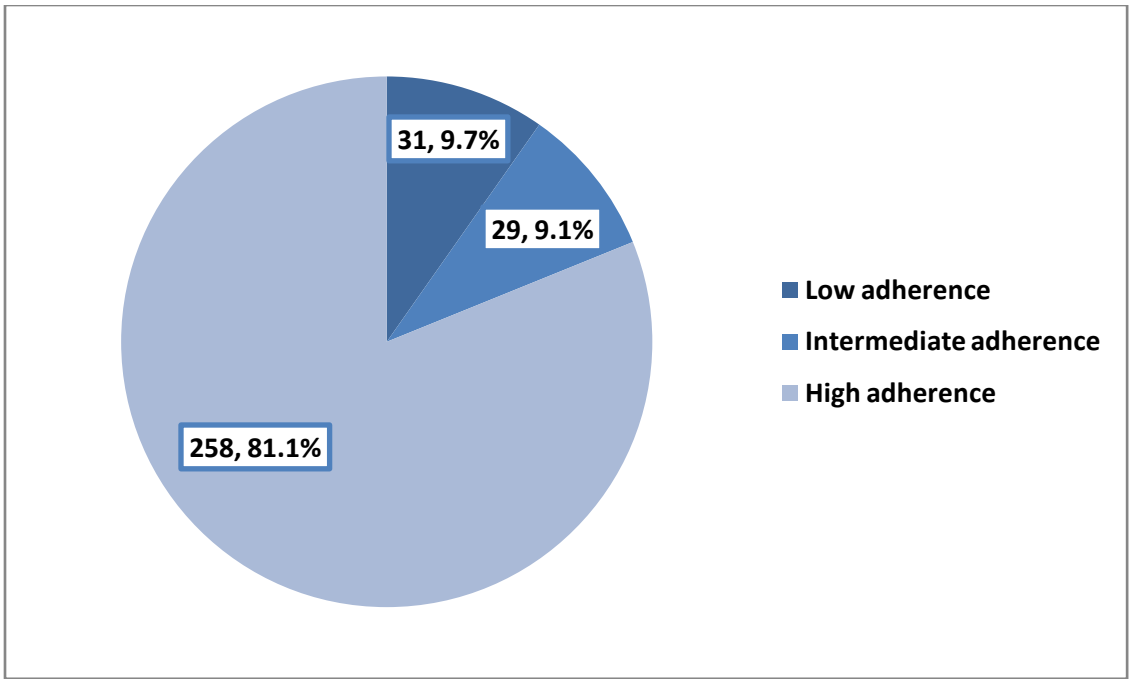

Figure 1:- Level of adherence to anti-epileptic medicationsamong patients with epilepsy.

Conclusion:-

In summary, most epileptic patients generally adhered well to their AEDs. However, a significant number of patients, especially those with frequent seizures, those who experienced adverse reactions to AEDs, and patients aged 41-50, showed low to moderate adherence. Therefore, it's important for physicians to encourage adherence to AEDs and be vigilant in monitoring for any potential adverse effects. Pharmaceutical industries should avoid the adverse effects of AEDs as much as they can.A further multi-centric longitudinal study should be performed for more clarification of the situation in Saudi Arabia.

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