A possible case of natalizumab-dependent suicide attempt: A brief review about drugs and suicide

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ABSTRACT

β-Interferon therapy is known to be a potential trigger of suicidal behavior, but this effect has not been previously reported for other multiple sclerosis (MS) treatments, such as, natalizumab. Here we report the case history of a 32-year-old woman affected by relapsing–remitting MS, who attempted suicide during natalizumab treatment. This case suggests that a suicidal ideation might be a rare side effect of natalizumab. Nevertheless, this case represents the first evidence of the new adverse drug reaction related to natalizumab treatment. We should alert clinicians to be aware of the possibility of paradoxical activation of suicidality during its therapeutic use. The main purpose of the present article is to use this case to review the possible relationship between suicidal behavior and drugs.

Key words: Antiepileptic drugs, anti-depressive drugs, multiple sclerosis, natalizumab, suicide

INTRODUCTION

An important cause of premature death is represented by suicide, especially in people/patients with psychiatric disturbances. In recent years, the US Food and Drug Administration (FDA) has warned that suicidal ideation or behavior may be an adverse effect of at least 130 prescription drugs, routinely used for indications such as asthma, smoking cessation, neuropathic pain, depression, and anxiety, among others.[1] However, an increase in suicidal ideation is observed in medical patients, especially those suffering from physical illnesses.[2] In fact, the psychological impact of suffering from severe diseases, associated with mood disorders such as anxiety and depression, represent an important risk factor for suicidal ideation in the medical patient population. Multiple sclerosis (MS) is one of the most frequent neurological diseases and is a cause of disability among the young population.[3] During these years, several studies have shown a higher suicide rate in patients with MS and have correlated suicidal behavior with a series of risk factors such as mood disorders, psychosis, high level of physical disability, social isolation, and younger age.[4-7] Here we report a case of a patient affected by a relapsing-remitting form of MS, who developed a suicidal ideation during natalizumab treatment.

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CASE REPORT

A 32-year-old woman was diagnosed with relapsing–remitting MS in 2001, displaying typical MS features on magnetic resonance imaging (MRI) and in the cerebrospinal fluid (presence of oligoclonal bands) according to McDonald's

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criteria. Initially, she was treated with subcutaneous high-dose interferon β-1a (44 mcg) thrice a week, for one year, and amitriptyline (25 mg/day), because she complained of migraine without aura and depression (Beck Depression Inventory score: 15). She was unable to tolerate the flu-like syndrome and she switched to glatiramer acetate for further three years. In October 2008, after discontinuation of glatiramer acetate due to adverse drug events (recurrent syncope), a significant progression in lesions was observed, on MRI investigation. In July 2010, the patient was admitted to our Clinical Neurology Department and she was commenced on natalizumab immunotherapy (300 mg every fourth week). At this point, she presented with an Extended Disability Status Scale Score estimated at 5 and a Beck Depression Inventory Score estimated at 4. We decided to continue the antidepressant therapy with amitriptyline (25 mg/every day) because she had benefit both in mood disturbance and migraine attacks (assessed on two attacks every month). After the twenty-fifth natalizumab infusion, she was brought into the Emergency Department, as she had collapsed next to an empty bottle of amitriptyline. She had a Glasgow coma scale score of 7 / 15, was tachycardic and twitchy. After a rapid sequence induction and intubation, she had benefit from gastric lavage. Unfortunately the toxicological assessment of dosage of drugs was not performed.

She was admitted to our Neurology Department and underwent a comprehensive clinical and laboratory investigation. In particular, the MRI examination did not show a progression of brain lesions, cerebrospinal fluid study was negative for JC virus, and anti-drug antibodies against natalizumab were not detected. A progressive multifocal leukoencephalopathy diagnosis was excluded and after psychiatric evaluation, a diagnosis was made of severe depressive disorder and psychosis. Indeed, as a precautionary measure natalizumab therapy was stopped, with improvement of psychosis after two weeks. On the basis of the Naranjo probability scale, we have documented a possible association between a suicidal attempt and natalizumab treatment, and we have reported this case as adverse drug reaction. Nevertheless, the exact contribution of amitriptyline and natalizumab to the genesis of suicidal attempts remains unclarified. We thought that natalizumab had induced suicidal ideation, because the depression disturbance was well-controlled by amitriptyline for several years and psychosis appeared after the introduction of natalizumab. However, it was not possible to exclude a synergic action of both drugs in the suicidal attempt.

DISCUSSION

Natalizumab and suicide attempts: A new possible adverse effect

This case is a symbol of how unexpected consequences can arise from our incomplete knowledge of the effects of drugs on behavioral aspects. WHO, for example, would have predicted how natalizumab, a monoclonal antibody targeting α-4 integrin on leukocytes (that was approved by the FDA and the European Medicines Agency as a monotherapy for highly active relapsing–remitting MS), would increase the risk of developing suicidal ideation, without causing notable progressive multifocal leukoencephalopathy.

After discontinuing natalizumab use in clinical practice, on the basis of three reports of progressive multifocal leukoencephalopathy, it is widely used for its therapeutic benefit, despite potential risks, which are reduced by long-term follow-up clinical studies and post-marketing observations, such as, appropriate patient selection and management recommendations. The overall incidence of serious adverse events associated with natalizumab treatment seem to be low and include serious liver injury, melanoma, and central nervous system (CNS) lymphoma.[8] If neurobehavioral and cognitive changes have been reported only in association with progressive multifocal leukoencephalopathy, several studies have reported an improvement of cognitive function during natalizumab treatment.[9] Actually, no literature data are available about psychosis or suicidal attempts during natalizumab treatment; our case could be the first evidence for a possible link.

Anti-depressive drugs and suicide risk: Is there a link?

New immunomodulatory therapies and the old non-immunomodulatory therapies belong to different pharmacological categories (such as anti-depressive, antiepileptics, and corticosteroids) and must be approached with caution in humans. In fact, numerous studies have examined exposures to individual drugs or drug classes and treatment-emergent suicidal behavior.

In particular, an increase in suicidality during anti-depressant treatment is an event so well known that it is referred to as the 'roll-back' phenomenon. On the basis of these considerations, it may be possible to speculate in our case that amitriptyline may have played a role, but literature data are discordant. In fact, Fergusson *et al*.[10] have found a two-fold increase in the risk of suicide attempts in users of selective serotonin reuptake inhibitors (SSRIs) compared to placebo or other interventions, but no difference in the risk has been seen with tricyclic anti-depressant (TCA) use. Conversely, Martinez *et al*.[11] have found no overall difference in the risk between SSRIs and TCAs, but observed an elevated risk of suicidality with SSRIs compared to TCAs, in patients aged 18 or younger. In 2003, the FDA had issued a public health advisory to call attention to clarify the occurrence of suicidality in pediatric and adolescent patients with depression, treated with anti-depressants. The FDA's actions have had an effect on the prescribing volume for patients younger than 18 years, the specialty mix of physicians treating patients younger than 18 years with anti-depressants,

and the type of medications used in treating depression. The FDA recently released results from an analysis that evaluated adult suicide and ideation data. The findings were mostly positive and suggested that anti-depressant drugs do not exacerbate suicidal thoughts in patients 30 years and older, but the suicide thoughts/ideations seen in the pediatric data extend to young adults up to the age of 25 years.[12]

Antiepileptic drugs and suicide: An intriguing relationship

In 2008, the FDA issued a new alert to healthcare professionals with regard to the risk of suicide for another class of drugs. In fact, the FDA again alerted clinicians to inform patients and their families regarding the statistically significant 1.80-fold increased risk of suicidality associated with all anti-epileptic drugs (AEDs). This was based on a meta-analysis study on 11 AEDs including carbamazepine, valproate, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide.[13] Moreover, literature data on this issue are conflicting. Other investigators[14] found opposite results: None increase the risk of suicide attempts in patients with bipolar disorder treated with AEDs compared to patients treated without AEDs, but a reduction of suicide attempt rates in patient with AEDs was observed. The question whether the FDA alert was a fire or a false alarm is still unsolved. In a review, Hesdorffer and Kanner[15] have highlighted very few studies that have been published and these studies showed a very low risk of suicidal ideation in patients treated with AEDs. Indeed, the authors have noted that a previous history of psychiatric disorder or a family psychiatric disorder is always present in cases reported with AEDs and suicidal behaviors.

These findings could reflect the natural course of illness more than the direct effect of AEDs. Nevertheless, the mechanism of action of the 11 AEDs was different; the FDA reassembled all these drugs as a unique entity because, "all share the ability to decrease seizure". The efforts of the scientific community have turned toward clarifying this issue. Recently, an expert consensus statement developed by an *ad hoc* task force of the Commission on Neuropsychobiology of the International League Against Epilepsy (ILAE) has been published. Although some (but not all) AEDs can be associated with treatment-emergent psychiatric problems that can lead to suicidal ideation and altered behavior, the actual suicidal risk is yet to be established, but it seems to be very low. Conversely the risk of stopping AEDs or refusing to start AEDs is significantly worse and can actually result in serious harm, including death, to the patient. On the basis of the findings, suicidality in epilepsy has a multifactorial pathogenesis; clinicians should investigate the existence of such risk factors and adopt the appropriate screening instruments. When starting an AED or switching between AEDs, patients should be advised to report to their treating physician about any change in mood or suicidal ideation.[16]

Corticosteroid withdrawal: A potential risk for suicide

Indeed not only drug use, but withdrawal of a drug can be a crucial period and may be involved in suicidality. In particular, it has been reported that discontinuation of long-term oral glucocorticoid therapy is associated with an increased risk of both depression and suicide, and a suicide attempt during the withdrawal period.[17] However, the question is about the higher risk of suicide in the population treated with drugs independent of the types or pharmaceutical classes of drugs. More recently, some articles have described that altered levels of chemokines in the cerebrospinal fluid and plasma have been found in persons who attempted suicide[18] and low plasma levels of the vascular endothelial growth factor (VEGF) have been found in cases of suicide.[19] Both conditions may be considered after natalizumab therapy, as possible contributions.

CONCLUSION

Although a large amount of literature data has been published speculating on the intriguing relationship between suicidal behavior and pharmacological agents, the neurobiological mechanisms have not yet been understood and still remain obscure. What, when, and why several drugs can be dangerous and are able to induce suicidality in some people, and how to assess the risk of suicide in drug users, are all unsolved questions. Moreover, emerging data from pharmacogenetic studies showing the gene effects on treatment response also seem to be promising, not only to clarify the neurobiological aspects but also to provide additional tools for a tailored therapy to reduce the risk of suicidal ideation and suicidal attempts in drug users.[20]

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