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Case report

Witnessing loss of consciousness during TMS – Syncope in contrast to seizure

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ABSTRACT

Objective: Transient loss of consciousness (T-LOC) can occur during transcranial magnetic stimulation (TMS). T-LOC during TMS can be caused by syncope or seizure. TMS operators explicitly screen participants and are also able to witness clinical manifestations of T-LOC during stimulation. Therefore they have direct access to information necessary to tell the two etiologies apart, if they are well trained on the clinical differences and not only sensitive to the potential risk of seizure induction. We here present a typical case of vasovagal syncope during TMS to contrast its clinical manifestations to that of seizures.
Method: We describe an event of T-LOC in a 21 year old healthy woman during single-pulse TMS. Screening, setting, clinical manifestations and advanced diagnostics are reported.
Discussion: Based on the detailed description of the case, we discuss why syncope is the most parsimonious etiology for the clinical picture observed in this participant. We provide information on typical clinical features of seizure that were particularly not observed. We also address potential benefits of further diagnostic tools. Additionally, we go into more parameters that can be useful to distinguish syncope from seizure.
Conclusion: TMS operators should be well aware of the differentiation of T-LOC in syncopal or ictal in etiology, because they witness T-LOC during TMS. By presenting a typical case of vasovagal syncope during TMS the report in hand provides necessary information and literature to do so.

1. Introduction

Transient loss of consciousness (T-LOC) is difficult to classify as syncopal or caused by seizure if it is not directly observed. Because transcranial magnetic stimulation (TMS) is always performed in the presence of an operator, T-LOC occurring during a stimulation session is witnessed in most cases. Nevertheless, there are difficulties in diagnosing the cause of T-LOC during TMS for several reasons. First, because operators are often not medical practitioners experienced in differentiating the two conditions (e.g., neurologists). Secondly, because operators are typically not explicitly trained by physicians to distinguish syncope apart from seizure. Instead, operators are often very sensitive to the potential risk of seizure induction as the most severe, albeit relatively uncommon, side effect during repetitive TMS (rTMS). In order to manage an occurrence of T-LOC appropriately, it is crucial to be aware of the possibility of inducing a seizure during stimulation. That prior knowledge itself, however, may result in a biased clinical classification of the adverse event. In that regard, reports describing the clinical picture of other causes of T-LOC, such as TMS-related syncope, are rare (Hadar et al., 2012; Sczesny-Kaiser et al., 2013; Gillick et al., 2015) and therefore awareness of this cause is low. We here present a typical case of vasovagal syncope during TMS to illustrate its clinical manifestations relative to that of seizures.

2. Case report

2.1. Screening

The participant was a 21 year old healthy woman. A screening questionnaire (Rossi et al., 2011) prior to participation in the experiment revealed no exclusion criteria for TMS. In particular, the participant did not take any medications that might lower seizure threshold and denied any personal or family history of

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epileptic seizures. The participant reported three episodes of T-LOC in the past that were classified as syncopal with high certainty (see discussion below). A non-diagnostic, structural magnetic resonance imaging scan one year prior to screening showed no pathology, especially no intracranial space-occupying lesion. The participant gave informed consent to this case report.

2.2. Setting

The stimulation took place as part of a cognitive-neuroscientific study that aimed at measuring behavior in a psychological experimental task after transient disruption of a brain area that is presumably involved in the cognitive process associated with the task. The experimental session was performed in a TMS research laboratory in a non-clinical setting, that was equipped with a MagProX100 stimulator (MagVenture, Hueckelhoven, Germany; CE-certificate 0543) and a medical chair that the participant was seated in (Greiner, Pleidelsheim, Germany). Two non-medical operators, trained and experienced with TMS stimulation, and trained in first aid and the management of side effects of TMS by a physician, were present. The session started with a measurement of resting motor threshold according to the Rossini-Rothwell method using a figure eight coil, standard coil orientation (anterior-medial direction of induced current), positioned over the left scalp and centered approximately 5 cm lateral/2 cm anterior from the vertex (stimulation of the right first dorsal interosseous muscle); biphasic single-pulses with at least 5 s between pulses (Rossini et al., 1994; also cf. Tranulis et al., 2006).

2.3. Clinical manifestation of T-LOC

On the day of the event, the participant appeared in good condition to the experimenters and reported well-being upon inquiry. After two single pulses (at 55% and 53% stimulator output) the participant reported that stimulation was different to what was expected, but was willing to continue. After the third pulse (at 53% stimulator output) the participant asked to stop the stimulation and subsequently had rapid loss of consciousness accompanied by loss of muscle tone and upward eye deviation. Stimulation was immediately terminated. The participant had no urinary or fecal incontinence, no tongue biting and no other physical trauma. Medical advice was sought. Consciousness was regained completely and spontaneously within 30–60 s. She was oriented, showed adequate formal reasoning and had no retrograde amnesia. Vital signs were in normal range (blood-pressure 120/80 mmHg, heart-rate 72/min). The participant laid down with her legs inclined. An emergency physician was contacted by the medical technical assistants.

2.4. Advanced diagnostics

The participant was transferred to the hospital after having been seen by the emergency physician as a precautionary measure. Physical and neurological examination, circulatory parameters, routine blood samples and electrocardiography showed normal results. Neither electroencephalography (EEG) nor neuroimaging was performed. The participant was dismissed from the hospital on the same day. Four days later a routine check-up at the general practitioner revealed no abnormality. The *Calgary Syncope Symptom Score* (Romme et al., 2009), which was additionally performed at our institute, indicated the presence of vasovagal syncope with a total point score of 3.

3. Discussion

3.1. Screening

The participant reported a history of T-LOC, unrelated to TMS, that was determined to be likely syncopal in etiology. Syncope is not an exclusion criterion for TMS. Nevertheless, it should be considered that syncope may emerge again during TMS. This is likely unrelated to the electrophysiological effects of TMS itself, but rather due to the procedure-associated stress (e.g., anxiety due to the knowledge of receiving a stimulation of the brain). Knowledge of this circumstance is critical, because in contrast to other procedures (e.g. blood sampling), T-LOC during TMS needs to be classified as syncopal or TMS-induced seizure.

3.2. TMS parameters

In rTMS shorter inter-train intervals, longer train durations and/or increased TMS frequency go along with increased risk of seizure induction (see Table 3 in Rossi et al., 2009 for safety limits). Although seizure induction is the most severe adverse event of TMS, incidence of rTMS-induced seizure is extremely low, especially if participants have no neurological disorder and are not on medication lowering seizure threshold (Rossi et al., 2009). Seizure induction in a healthy individual by single-pulse TMS at 53% stimulator output is extremely unlikely (also see Pascual-Leone et al., 1993). To our knowledge, there is only one report that described seizure induction by single-pulse TMS (Kratz et al., 2011) and diagnosis of seizure remains questionable for that case.

3.3. Clinical manifestation

The case in hand is particularly suited to present typical clinical manifestations of syncope in contrast to seizure, because the participant not only experienced T-LOC during single-pulse TMS, but also prior to participation in the experiment and therefore not TMS-related. Medical history assessment revealed that all events of T-LOC prior to TMS were preceded by malaise or associated with emotion or orthostatic stress (i.e., prior to taking a blood sample and after long standing, during a common cold and nocturnal micturition and during the administration of an inoculation). After T-LOC, consciousness was consistently regained within seconds. These are all criteria in line with vasovagal syncope (Moya et al., 2009). On the other hand, typical clinical signs of seizure in previous events of T-LOC were denied, such as tongue-biting (Brigo et al., 2012), urinary incontinence (Brigo et al., 2013), prolonged loss of consciousness (i.e. minutes, Jenssen et al., 2006) and postictal state (disorientation, retrograde amnesia etc., Fisher and Schachter, 2000). Reported episodes of T-LOC were not preceded by sleep deprivation, flickering lights or intoxication (e.g. alcohol); events that are considered as seizure triggers (Koepp et al., 2016). For the current event of T-LOC during TMS, none of the above-mentioned clinical manifestations of seizure were present. However, as in the reported previous case history, the event was preceded by slight malaise and mild anxiety as well as constricted field of vision and a feeling of warmth (as retrospectively affirmed by the participant and hence not directly accessible during the event of T-LOC). In contrast to previous episodes, though, this time T-LOC was directly witnessed. This is an important point, because neurological/motor symptoms typically related to most seizure types (Crompton and Berkovic, 2009) could be excluded this way. These are specifically (*i*) (tonic-) clonic movements, that is, a phase of tonic posturing (stiffening) and/or a phase of clonic jerking (twitching) of the muscles, (*ii*) vocalisations and (*iii*) automatisms (e.g., repetitive raising and lowering of an arm as well as head turn-

ing as in Bonelli et al., 2007). Such neurological phenomena are usually not present during syncope. If nonetheless present, such as in convulsive syncope, these motor symptoms are still preceded by syncope-typical features (e.g. lightheadedness, pallor, diaphoresis; also see Romme et al., 2008), usually do not include clear clonic features and are of short duration (<15 s) (da Silva, 2014). Upward eye deviation as observed during T-LOC in this participant can be classified as a symptom of syncope (Lempert and von Brevern, 1996).

3.4. Consideration of age and gender

Age can be an additional marker when distinguishing syncope from seizure. Vasovagal syncope is associated with younger age (Romme et al., 2008) while the incidence of epilepsy is lowest between age 20 and 40. However, this criterion can only be used to classify past T-LOC (prior to TMS), because previously reported cases of seizures in TMS predominantly occurred in participants within age 20–40. Additionally, this case report adds to the previous literature that only reports TMS-related syncope in female participants (Figiel et al., 1998; Hadar et al., 2012; Sczesny-Kaiser et al., 2013; Gillick et al., 2015). The reason for the predominance of female gender remains speculative: Incidence of syncope is slightly higher in women compared to men in some studies (Romme et al., 2008), other authors report no effect of gender on the incidence of syncope in the general population (da Silva, 2014). Many TMS studies in healthy subjects are actually performed in men only. The predominance of female gender is also true for case reports on TMS-related seizures.

3.5. Clinical assessment

Although the *Calgary Syncope Symptom Score* (Romme et al., 2009) indicated the presence of vasovagal syncope, specificity of the score is low. However, the use of scoring schemes (e.g. also, Sheldon et al., 2002) can be beneficial in differentiating seizure from syncope in T-LOC during TMS. Our participant was admitted to the hospital. Note that we do not suggest that indiscriminate admission of participants with T-LOC to the hospital is necessary, but rather that medical advice should be sought, and a joint decision on further proceedings made based on the individual circumstances. In the current case of T-LOC operators were not sufficiently sure to link the observed clinical manifestations to either syncope or seizure. The emergency physician neither witnessed the event of T-LOC, nor was he aware of the relative risk of seizure induction by TMS. Those circumstances most likely resulted in the admission of the participant to further overlook the case. There was no significant concern that the event was ictal in etiology. If there was high suspicion for an epileptic seizure, an EEG would be indicated for the evaluation of a first T-LOC event, would have management implications and could have been performed with moderate yield even 24–48 h after the occurrence of T-LOC, that is, after admission to the hospital (King et al., 1998; Krumholz et al., 2007). Magnetic resonance imaging (MRI) should be performed when suspecting T-LOC as ictal in etiology to further aid diagnosis and treatment (King et al., 1998; Krumholz et al., 2007). An MRI-scan acquired in a non-clinical study setting without proper MRI sequences and long time before the event is not sufficient in that regard for both reasons.

4. Conclusion

In summary, the most parsimonious etiology of the case of T-LOC presented here is vasovagal syncope. Screening, clinical manifestation and clinical assessment yielded no significant concern that the event of T-LOC was ictal in etiology. Note that an atonic seizure or focal seizure with impairment of consciousness cannot be ruled out entirely, but are very unlikely. The differential diagnosis of an absence seizure (as documented in the hospital's medical report) is not consistent with the observed clinical manifestation. TMS operators explicitly screen participants and are also able to witness clinical manifestations of T-LOC during stimulation. Therefore they have direct access to information necessary to tell the two etiologies apart. The report in hand provides necessary information and literature to do so and could therefore reduce false association of T-LOC with seizure. However, if in doubt, medical advice by a physician is to be sought. We did not consider the differential diagnosis of cardiogenic syncope in this case report, because it was highly unlikely (young woman; no history or family history of cardiac disease; no sudden occurrence of syncope, that is, "drop attack"; electrocardiography showed normal results; among other things; also see Dohrmann and Cheitlin, 1986).

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Conflict of interest

The authors declare no competing financial interests.

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