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BIZARRE BEHAVIOR DURING INTRACAROTID SODIUM AMYTAL TESTING (WADA TEST)

Are they predictable?

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ABSTRACT - The intracarotid sodium amytal test (ISAT or Wada Test) is a commonly performed procedure in the evaluation of patients with clinically refractory epilepsy candidates to epilepsy surgery. Its goal is to promote selective and temporary interruption of hemispheric functioning, seeking to define language lateralization and risk for memory compromise following surgery. Behavioral modification is expected during the procedure. Even though it may last several minutes, in most cases it is subtle and easily manageable. We report a series of patients in whom those reactions were unusually bizarre, including agitation and aggression. Apart of the obvious technical difficulties (patients required physical restraining) those behaviors potentially promote testing delay or abortion and more importantly, inaccurate data. We reviewed those cases, seeking for features that might have predicted their occurrence. Overall, reactions are rare, seen in less than 5% of the ISAT procedures. The barbiturate effect, patients' psychiatric profiles, hemisphere dominance or selectiveness of the injection were not validated as predictors. Thorough explanation, repetition and simulation may be of help in lessening the risk of those reactions.

KEY WORDS: refractory epilepsy, Wada test, sodium amytal.

Reações bizarras durante o teste do amital sódico intracarotídeo (TASI ou Teste de Wada): é possível prevê-las?

RESUMO - O teste do amital sódico intracarotídeo (TASI ou teste de Wada) é procedimento comum na avaliação de pacientes portadores de epilepsia clinicamente refratária candidatos a cirurgia de epilepsia. Tem por objetivo promover interrupção seletiva e temporária da função hemisferial, definindo lateralização de linguagem e risco de comprometimento de memória no pós-operatório. São esperadas mudanças comportamentais durante o teste, as quais podem durar vários minutos, porém, em geral, são sutis e facilmente manejáveis. Relatamos uma série de casos em que ocorreram comportamentos pouco usuais, bizarros, incluindo agitação e agressividade. Estes comportamentos comprometem o teste (paciente deve ser contido), podendo levar a atrasos ou mesmo abortamento do mesmo, além de produzir dados menos confiáveis. Os casos foram revisados, visando a definição de preditores de sua ocorrência. Estas reações são raras (5% dos casos). Efeito barbitúrico, perfil psiquiátrico, dominância cerebral e seletividade da injeção não puderam ser validados como preditores. Explicações detalhadas, repetição e simulações podem ser utéis na prevenção deste tipo de ocorrência.

PALAVRAS-CHAVE: epilepsia refratária, teste de wada, amital sódico.

Behavioral modification is expected during the intracarotid sodium amytal test (ISAT) or Wada Test[1,2]. That is frequently seen either shortly after the injections or during the recovery time, and may last several minutes. It is generally subtle and easily manageable. At times, however, those behavioral changes may be rather bizarre, concurring with inappropriateness, agitation and even aggression[3]. Although somewhat rare, those reactions are frequently misleading, as they promote testing delay, inaccurate data or even testing abortion.

We report a series of such peculiar cases, along with a literature review, seeking for features that might help in predicting their occurrence, as future reference for ISAT candidates.

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METHOD

Between 1997 and 2002, 129 patients, diagnosed with refractory epilepsy, underwent a comprehensive non-invasive evaluation at the Epilepsy Program, Neurology Service, Hospital de Clinicas, Federal University of Parana, Brazil. As part of their evaluation, 81 patients were subjected to the ISAT.

At our institution, we use an ISAT protocol that is essentially a modified version (adapted to language and cultural variations) of the ISAT Protocol utilized at the Minnesota Epilepsy Group, Saint Paul, MN. In brief, a pre-test is presented to each patient a few hours prior to the test itself. This would be just a simulation in order to get the patient acquainted to the test routine. The test properly starts with a standard placement of a femoral catheter, plus a cerebral angiography, which is performed while looking for eventual anatomical variations or vascular anomalies. We then use selective carotid injections consisting of a 125mg boluses of sodium amytal (SA) plus 50mg in reserve, if necessary. An electroencephalogram (EEG) is always performed during the procedure. A series of items is then presented during the anesthetic effect. The latter is measured by a combination of both the level of contralateral motor deficit and the most significant EEG changes, i.e., ipsilateral slowing plus the crossover phenomenon. Crossover is defined as the time elapsed from the beginning of the injection (promoting ipsilateral slowing) to the presence of slowing on the contralateral hemisphere. Memory recall is assessed during the recovery time. Injections are always 30 minutes apart.

Although the vast majority of patients perform really well during the ISAT, there are exceptional cases presenting very impressive behavioral changes. Their cases were retrospectively studied, including seizure history, video-electroencephalography (VEEG) data and psychiatric profile, along with their performance during the test itself, including clinical presentation and the EEG data seeking for features that may have predicted these kinds of reactions, as a future reference for potential ISAT candidates.

The consistent features were analyzed as to determine their potential as markers in predicting those reactions.

RESULTS

Five (5.1%) out of the 81 patients who underwent the ISAT developed bizarre behavior during the test. The group consisted of 2 male and 3 female patients, with a mean age of 29(13-38). Four patients had temporal lobe epilepsy with MRI proven mesial temporal sclerosis (MTS) and one patient had a right parietal glioma.

All bizarre behaviors were limited to a maximum of 15 minutes and none of the patients had any recollection of the facts afterwards. Their cases are described in detail below.

Patient 1. A 13 year-old, right handed, somewhat introspective young man, diagnosed with refractory lesional parietal lobe epilepsy related to a right parietal glioma. There was no formal diagnosis of mood disorders. Seizures happened on monthly basis, mostly of the secondarily generalized type. VEEG recording showed right parietal interictal spikes and suggested seizure lateralization on the right cerebral hemisphere. A lesionectomy was planned as the surgical approach. At that point in our series all epilepsy surgery patients were subjected to ISATs. His pre-test was unremarkable and the catheter positioning was carried out with no intercurrences. Cerebral vascular anatomy was preserved. Following the first injection (right internal carotid bolus of 125 mg of SA) the patient was capable of talking, developed a massive left hemiplegia and performed well, being cooperative during the items presentation. As the hemiplegia subsided he became disinhibited and talkative, displaying a seductive behavior both verbally and physically, with attempts to caress one of the female members of the team. Interestingly, cooperation was still adequate during items recovery phase. With the injection on the left side, he became aphasic and developed a right hemiplegia. He was very agitated. As the hemiplegia and aphasia slowly subsided, he developed extreme anxiety and a tremendous feeling of fear. He then became overwhelmingly agitated, escalating to a point in which physical restrain was required. He cried out for help repeatedly during this period ("let me go, for Christ sake"). This episode lasted 14 minutes and it was of such magnitude that it significantly interfered with the test conduction. There was a lack of cooperation but not to the point of invalidating the entire injection. EEGs on both injections were substantially superimposed by muscle and movement artifacts. The right injection, however, disclosed better lateralization of the EEG slowing, whereas on the left side diffuse EEG changes were noticed almost immediately after the injection, suggesting an early crossover.

Patient 2. A 30 year-old, right handed female, diagnosed with refractory mesial temporal epilepsy, related to right MTS. The patient was highly dependent on her husband and the couple sustained a long lasting history of infertility. The latter turned into a very delicate matter as she partially blamed it on her antiepileptic drugs (AEDs). Plus, the constant fear of finally getting pregnant under the use of AEDs constituted an additional limitation to her treatment compliance. The couple never underwent formal investigation for infertility and remained childless until this point of follow-up. Thus, she was also diagnosed with a mood disorder (depression). Seizures were predominantly nocturnal, complex partial with rare secondary generalization. They tended to occur every 2 weeks, in spite of polytherapy .VEEG recording showed right temporal interical spikes and seizures coming from the right (mesial) temporal lobe. An ISAT was requested aiming at a classic non-dominant temporal lobectomy. The pre-test was unremarkable and the catheter positioning was carried out with no intercurrences. Cerebral vascular anatomy was preserved. The right internal carotid artery was injected first (125mg of SA) and a second bolus (50mg of SA) was found to be necessary due to incomplete contralateral hemiplegia. Following this second bolus, she tilted her head backwards and became confused for about four minutes. That was replaced by extreme agitation accompanied by an expression of fear. She reported a feeling of imminent death, and verbalized traumatic events that took place in her childhood. The exact nature of those could never be entirely defined. She then started screaming out loud, asking for help for about six minutes. She cried out mostly her husband's name repeatedly. She had to be restrained by the staff members, in order to prevent complications involving the catheterism. The core of this episode lasted close to 10 minutes. Even after physical restrain was imposed she remained confused and agitated for several minutes and ultimately the test had to be aborted. There was no injection on the left side. There was partial prejudice to EEG inter-

pretation due to muscle and movement artifacts. However, an almost immediate diffusion of the EEG slowing was noticeable following the injection. There was never any clear lateralization throughout the recording.

Patient 3. A 38 year-old, left handed (in spite of reports suggesting that he may be ambidextrous), very introspective young man. He was clearly overprotected, being accompanied by his mother to all clinic visits and most likely to all his (rare) social functions. He was diagnosed with a mood disorder (depression) and alternated times on and off antidepressant medication. He also displayed traces of an obsessive-compulsive behavior. The latter was thought to be mild in its presentation, causing little additional limitation to his already restricted environment. He was diagnosed with refractory mesial temporal lobe epilepsy related to left MTS. Seizures usually happened a weekly basis, mostly complex partial with generalized tonic-clonic episodes on occasions, in spite of polypharmacy. VEEG recording showed interictal spikes exclusively on the left temporal lobe and seizures coming from the left mesiotemporal region. An ISAT was requested and a standard dominant lobectomy was planned. The pretest was unremarkable and the catheter positioning was carried out with no intercurrences. Cerebral vascular anatomy was preserved. After 125 mg of SA were delivered to the left cerebral hemisphere the patient became aphasic and displayed massive right hemiplegia. As he recovered from both deficits, he became excessively disinhibited and declared that "he had a confession to make". At this point he was agitated, very talkative in a particularly loud manner, articulated and clearly stated "special feelings" (as in "being in love") towards one of the staff members, a young female resident. The disinhibition lasted a few minutes leading to partial compromise of the final part of the presentation and the recovery items, as he would not focus adequately on the test. Much to our team surprise, the same set of events was reproduced with the right injection, but in a more subtle fashion. That included reassurance of the emotional attachment to the same team member. There was no aphasia but, left hemiplegia was present. The EEG on the left injection showed an almost immediate crossover and was partially superimposed by muscle and movement artifacts. On the right side, the EEG suggested a much more selective injection, with right sided slowing and a later crossover, noticed close to 90 seconds following the injection.

Patient 4. A 32 year-old, right handed female, diagnosed with refractory mesial temporal epilepsy related to MRI proven left MTS. Seizures happened every two months and compliance seemed adequate to a combination of AEDs. She is an extremely introspective, almost laconic patient who was also treated for depression (fluoxetine 20mg qday), with poor results. She was always alone during her clinic visits and family support, as a whole, was rather questionable. Even during the decision process involving her surgery, the only family member present was and adolescent son, who was also very shy. VEEG recording showed rare left temporal interictal spikes and one single seizure clearly recorded from the left (mesial) temporal region. After injection of 125mg of SA on the left internal carotid, she developed an aphasic status that lasted around 4 minutes, accompanied by massive right hemiplegia. As she slowly recovered, copious crying took place, during which she described (in very a fragmented form) an episode of sexual abuse, perpetrated by her father during her childhood years. She remained inconsolable for several minutes and ultimately this behavior delayed the items recovery part of her test. The injection on the right side, with the patient calm and cooperative, was uneventful. EEG on the left injection showed very early crossover (within 10 seconds of the injection), markedly associated with muscle and movement artifacts. On the right side, the injection was considered selective, with slowing limited to the injected side for about 230 seconds before spreading to the opposite hemisphere.

Patient 5. A 40 years old, right handed female, diagnosed with refractory mesial temporal epilepsy, related to left MTS. In addition, she displayed a very introspective behavior, being highly dependent on her husband to virtually all decision processes. A depressed mood was also noticed and she was tried on antidepressants with poor compliance. There was also a suggestion of non-epileptic seizures and on two occasions spells consisting of unresponsiveness were recorded without significant EEG changes. The diagnosis of mixed (epileptic and non-epileptic seizures) was established on that basis. As evidence suggested that the legit seizures were truly intractable the patient met criteria to undergo a non-invasive pre-surgical protocol, including an ISAT. Following the left injection (125 mg of SA) she evolved into an aphasic state plus right hemiplegia, with both conditions lasting close to 5 minutes. She then became disinhibited and started talking in a childish fashion. A nervous laugh and inappropriate jokes were also part of this behavior. She became uncooperative for the test purpose to a point in which mild restrain was required in order to avoid problems with the femoral catheter. Shortly afterwards she became verbally aggressive towards the team members. The set of events just described took extra 5 minutes. Testing for items recovery was finally possible but cooperation was still compromised. The injection on the right side was uneventful. The EEG on the left injection showed early crossover, occurring about 10-15 seconds after the injection, when slowing was clearly seen on both hemispheres. On the right side, the crossover was very delayed, occurring only after 280 seconds, translating a much more selective injection.

DISCUSSION

Wada testing is a commonly performed procedure in the comprehensive evaluation of patients with refractory epilepsy enrolled in the surgical evaluation, more so in patients who are diagnosed with MTS[4]. Its goal is to promote selective and auto-limited blockade of hemispheric functioning with the purpose of defining risk stratification for memory compromise related to the surgical procedure. The test was conceived by Juhn Wada in 1949 for the evaluation of patients submitted to shock treatment for psychosis and later it was found to be helpful in determining language dominance[5]. The original procedure was modified by the Montreal Neurological Institute so that it could also evaluate hemispheric memory functioning and was standardized as part of the evaluating protocol for epilepsy surgery[6].

Effects commonly related to the injection of SA include ipsilateral negligence[7], hemiplegia related asomatognosia, anosognosia[8] and limb phantom movements[9]. With right hemisphere anesthesia reactions such as euphoria and indifference can be elicited a few minutes after injection[10], whereas more dramatic, impressive reactions follow left hemisphere inactivation[3,11].

Emotional and/or behavioral side effects of varying intensity may happen, but most of the times they do not prevent further testing[12]. Mild emotional reactions due to disinhibition are quite common. Conversely, according to Masia et al. intense and severe emotional reactions are uncommon, happening in close to 2.5 to 5.4 % of all patients, without clear gender predominance; such strong reactions might be due in part to disinhibition itself. In addition, manipulation of the inguinal region might evoke memories of sexual abuse and/or other traumas similar in nature[3].

In this small series 2 patients showed evidence for epileptogenic zones on the right (non-dominant) and 3 on the left cerebral hemisphere. Further analysis of our own series of 81 ISATs disclosed additional 31 patients with epileptogenic zones related to the non-dominant (i.e, the right) hemisphere and 45 patients with seizure origin on the dominant (i.e, left) hemisphere, none of whom presented with bizarre behavior during their ISATs. Therefore, the lateralization of the epileptogenic zone does not seem to particularly predispose to a higher chance for complications during the ISAT (Fisher's exact test p=0.67).

Four patients displayed a tendency or an established diagnosis of a mood disorder (depression). One could be tempted to consider a trend towards depression as marker to potentially complicated tests. However, depression is simply too prevalent in refractory epilepsy patients in general to be considered an exclusive feature to complicated ISAT procedures. Figures as high as 62% or more are commonly reported as incidence of depression in clinically refractory epilepsy populations[13].

The typical clinical responses to dominant hemisphere injections (i.e., clear cut aphasia and contralateral hemiplegia) were obtained in all but one patient, in whom the test was prematurely interrupted (Patient 2). Thus, the initial clinical presentation itself was not particularly impressive, as to alert the examiners towards unexpected reactions.

In our 5 cases, 9 injections were performed (5 right, 4 left), leading to good EEG lateralization in 4 and very early crossover in 5 injections. Four out of the five non-selective injections on basis of the EEG analysis were performed on the dominant hemisphere (Fischer's exact test p=0.047). We reviewed 93 injections (46 right, 47 left) in 50 patients subjected to ISATs in whom no bizarre reactions were observed. Selective injections were obtained in 53 patients (30 right, 23 left) and early crossover was seen in 40 patients (16 right, 24 left) (Fischer's exact test p=0.048). These figures suggested that non-dominant injections tend to be more selective when compared to dominant ones. Nonetheless, this particular feature was observed in both groups (with and without bizarre behavior), which does not support the hypothesis that an early crossover in dominant injections could be of help in predicting problematic tests.

Finally, one has to consider the SA, itself. Barbiturates are capable of producing all levels of CNS mood alteration, from excitation to mild sedation, hypnosis, and deep coma. They may depress the sensory cortex, decrease motor activity, alter cerebellar function, and produce drowsiness, sedation, and hypnosis. According to Cournos and Cabaniss, SA specifically can be valuable as a sedative during the interview to produce disinhibition and allow the patient to speak more freely or access otherwise unavailable memories, in the scenario of difficult psychiatric consults[14]. Thus, the reactions described above may be just a small part of a broader universe of well known yet, unpredictable side effects of barbiturates.

CONCLUSION

Bizarre reactions during the ISAT are rare, probably occurring in less than 5% of all tests. Both the incidence and main features of such behavior observed in our series match similar cases described in the literature. Likewise, neither ours nor the patients reviewed from other series presented with a clinical profile that allow anticipation of their impressive reactions to the tests. Lengthy detailed explanations plus repetition and simulations may be of help in trying to minimize the anxiety related to an ISAT, as well as, any other invasive, prolonged and intellectually laborious testing.

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