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RESEARCH ARTICLE

Havana Syndrome: New Recommendations and Enrollment Criteria for a Shared Study of Possible Cases

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ABSTRACT

Background: From November 2016 to the summer of 2021, some U.S. diplomats and their family members residing in Havana and other locations, including China, Russia, Colombia, Switzerland, and France, reported the sudden onset of auditory, vestibular, and neurological symptoms. The aim of this study is to define enrollment criteria for patients with a possible diagnosis of Havana Syndrome.

Methods: This study, through a review of the scientific literature, proposes the definition of criteria for proper enrollment of patients with a possible diagnosis of "Havana Syndrome".

Results: In view of the increasing number of cases, their wide geographic distribution, and the lack of certainty regarding etiopathogenesis, it is essential to propose a strategy for sharing case histories.

Conclusions: A correct enrollment of patients is crucial since specialists can then disclose new strategies for the study of case histories and for a clear definition of the diagnosis. This way, it will be possible to have a wide discussion of clinical and epidemiological results among specialists in different medical, engineering, and intelligence disciplines.

Keywords: Havana syndrome, recommendations, criteria, diagnosis, enrollment, symptoms

INTRODUCTION

The purpose of this study is to define, through a literature review, enrollment criteria for patients with a suspected or possible diagnosis of Havana Syndrome.

The authors also analyzed the etiological hypotheses of the so-called Havana Syndrome.

Between November 2016 and 2017, several U.S. Embassy and Canadian Embassy staff members serving in Havana reported the occurrence of abnormal sensory and cognitive perceptions, associated with symptoms such as tinnitus, dizziness, nausea, and headache¹.

The first case was described by an employee of the U.S. Embassy in Cuba who, in 2016, woke up during the night with a sudden sharp pain and a feeling of pressure in his face. He reported hearing a loud piercing sound in only one ear, with the subsequent onset of acute dizziness symptoms accompanied by nausea². Clinical observation over the next few days confirmed possible but unclear vestibular dysfunction and highlighted the subsequent onset of cognitive impairment¹.

Subsequent to 2017, new cases involving employees of the U.S. Consulate in Guangzhou, China, were reported with signs and symptoms overlapping with known case reports.

Although not taken into consideration from a scientific point of view, the latest reported cases were found in the summer of 2021 in Geneva and Paris; other geographical areas affected are Russia, Eastern Europe, Colombia, and Washington³.

Many hypotheses have been put forward in the literature to explain these clinical cases. These include vestibular migraine, pesticide poisoning, and "acoustic attacks" through the use of devices capable of producing sounds at a high level and such as to cause damage to the auditory system¹. Regardless of the hypotheses put forward, the theories described so far do not seem to be acceptable and agreeable. In fact, only US federal employees or their relatives were affected. A specially constituted scientific committee published a detailed medical-technical report in "The National Academies of Sciences, Engineering, Medicine." Evidence of unusual clinical features and the circumstances of the onset of symptoms immediately led to media speculation regarding possible causes.

HYPOTHESES DESCRIBED IN LITERATURE

Technological systems often represent a real threat to health when viewed from a harmful perspective⁴. After the invention of radio, it was widely believed that invisible waves caused disease, or that the spread of computer terminals caused birth defects and miscarriages⁵. It was also hypothesized that microwave ovens and Wi-Fi were able to increase the risk of brain tumors⁶.

Another historical example was questioning the possible damage caused by using trains as a new means of transport. The London surgeon Herbert Page stated that in several cases of train accidents there was no damage to the spinal cord and this led him to the conclusion that "only the fright" generated the symptoms.

Also, musical instruments were the object of convictions concerning the onset of health problems; it was assumed a relationship between the production of sounds and the onset of neurological symptoms. Karl Röllig, a harmonica player, reported to have experienced a concatenation of disorders that he attributed to the harmonica itself⁷. Disorders ranged from nervousness to muscle spasms, dizziness, tremors, and hallucinations, to seeing ghosts and perceiving threatening noises.

People domiciled near wind turbines have claimed that the noise generated by the movement of the blades has made them ill⁸. Researchers working on the topic have speculated that the effects may be accounted for by the possible onset of mass psychosis. A definite causal link between the series of illnesses indicated in the vicinity of wind turbines and the sound reproduced by them is not described⁹. This has been considered as in favor of a psychogenic hypothesis.

The conclusion drawn by researchers is that the perception of such noises, if unbiased, does not lead to the onset of any symptoms.

In 2009, some authors made it known that a very small proportion of people domiciled near wind turbines manifested health problems related to stress caused by persistent noise perception with no direct causal relationship to it. There is no scientific evidence to show that sound below the minimum limit of human hearing has a negative effect on health⁸.

Relative to the events that occurred in Havana, the reported clinical symptomatology varied widely among those affected¹⁰. Differences are given by the intensity of signs and symptoms, type of onset, and prognosis. The collection of clinical data, although partial and not shared, has therefore allowed to exclude from the beginning a viral, bacterial or of toxic exogenous exposure etiology because of the variability in the onset and intensity of some symptoms¹.

To date, no convincing hypothesis has been documented in the literature regarding the selective capacity that an exogenous substance would have in affecting only subjects of certain nationalities and employed exclusively in federal offices, or even that it could affect their relatives⁶. The onset and persistence of symptoms have occurred in well-circumscribed locations, such as the Hotel Capri and the Hotel Nacional de Cuba, as well as in the homes of U.S. and Canadian

diplomats who have reported the appearance of symptoms¹¹.

Double-blind clinical studies have shown that simulated exposure to electromagnetic fields determines in some cases the exact same symptoms reported by subjects affected by a possible Havana Syndrome¹². The onset of a "placebo" type effect is one of the hypotheses that has been suggested in the literature. Among the etiopathogenetic hypotheses most represented in the literature about the symptoms experienced by subjects affected by Havana Syndrome there is that of a mass psychogenic illness that probably originated from the news that circulated about "harmful health attacks" produced by an unknown sound device¹³.

REVIEW OF THE LITERATURE

During the period between November 2016 and the summer of 2021, unexplained symptomatology was documented in 25 diplomats at the U.S. Embassy in Cuba, more specifically in Havana². The subjects experienced a number of sudden symptoms, and the State Department subsequently stated that "the reported symptoms are medically confirmed." The following have been documented: headache, dizziness, nausea, fatigue, difficulty concentrating, memory loss, confusion, disorientation, difficulty walking, insomnia, sensitivity to sound, ear pain, feeling of pressure in the ears, tinnitus, and symptoms similar to a brain injury¹¹.

The most important clinical aspects described by U.S. Department of State personnel in Havana were the nature of the onset and the initial characteristics; the sudden perception of a loud sound, a feeling of intense pressure or vibration in the head, and pain in the ear. Most individuals reported that the sound or these other sensations seemed to come from a particular direction and were only perceived when the individual was in a specific spatial location. Several subjects also reported sudden onset of tinnitus, partial hearing loss, dizziness, unsteady gait, and visual disturbances¹⁴.

Not for all subjects involved, however, there was a chronic evolution. In some cases, the onset was described as biphasic. Case studies were, therefore, heterogeneous also with reference to the evolution of symptoms¹. With regard to chronic evolution, since the first cases, possible involvement of both the cerebral cortex and limbic structures has been considered. The first consideration was that the neurological symptoms were not completely consistent with the vestibular tests subsequently performed and were not related to possible brain damage. One of the hypotheses initially proposed was that of the onset of an accommodation or response system to an initial brain insult.

Among the certain clinical data is notable the presence of the same symptoms in diplomats staying at the Hotel Capri and at the Hotel Nacional de Cuba or at their homes with the occasional involvement of their relatives³.

On August 9, 2019, thus not long after the news of the Havana Syndrome had been publicly announced, about 20 American tourists approached the Associated Press in order to report that in the same way as the U.S. diplomats, they too had experienced unusual noises and had been sick after staying at the Hotel Capri and the Hotel Nacional de Cuba in recent years. In the month following this report, a U.S. Embassy employee and his wife were evacuated from Tashkent, Uzbekistan, after reports of health problems related to the appearance of an undefinable sound².

U.S. government medical personnel initially speculated that the use of a sound device might be involved. Some acousticians and human health experts agreed that the source responsible for the symptoms experienced in Cuba was not an "acoustic attack" but another cause¹⁵.

Professor Timothy Leighton of Ultrasonics and Underwater Acoustics stated that in order to generate an ultrasonic beam that has the ability to hit someone at a distance of 50 meters, one would need a device the size of a car. The impact, however, would be limited and could probably only generate difficulties in concentration and an anxious state¹⁶. Psychoacoustics specialist Joseph Pompei states that "brain damage and concussions, are not possible" as to generate an effect of this magnitude, someone "would have to submerge their head in a pool lined with very powerful ultrasonic transducers."

Douglas H. Smith performed a few studies in MRI that highlighted widespread brain injury consistent with trauma without it occurring, evidence later re-evaluated and not confirmed¹⁷. In this sense, the literature documented a neuroimaging study where 40 subjects with typical symptoms of a possible Havana Syndrome were evaluated with MRI. The same subjects were then compared with a healthy population of 48 people. This comparison did not confirm evidence of significant brain changes consistent with the symptomatology described by the subjects involved.

The open journalistic and non-scientific sources we have considered have always highlighted two factors that can be summarized in the presence of "mild brain trauma" and "white matter changes" in the brain. The two factors documented by neuroimaging are, however, very common in diseases of the central nervous system and have never been put in a certain relation with the symptoms described by the subjects studied².

In addition, the scientific literature, to date, has in no way confirmed a certain relationship between

sound wave administration and white matter changes or evidence of trauma referable to sound perception¹⁸.

In 2018, the U.S. Department of State conducted another recall of its deployed personnel, this time in China, after reports of approximately 11 Americans reporting hearing changes and neurological symptoms similar to those manifested in personnel at the Guangzhou, Shanghai, and Beijing consulates.

Claims of an acoustic attack have caused disbelief among physicists and medical experts as to how individuals who were inside hotels or in their homes could have been the objective of targeted acoustic waves¹⁹. The instruments known to date as "acoustic weapon", in addition to being bulky and difficult to manage, do not have the ability to generate the cluster of symptoms as reported in Cuba and elsewhere.

Some military specialists dealing with acoustic weapons have expressed the opinion that: "high-intensity acoustic energy in the audible, infrasonic, or low-frequency range is unlikely to result from a device suitable for use as a nonlethal weapon." Human hearing ranges from 20 to 20,000 Hz while infrasound is below 20 Hz. It is therefore evident the difficulty in producing effective instruments in the targeted diffusion of these sound waves. Sound waves above 20,000 Hz, defined as ultrasound, fade quickly with distance; for such sound to be effective in generating clinical symptoms, it would require direct contact between device and human target. Some police forces use long-range acoustic devices, known as "sound cannons," for their ability to produce loud noises in order to disperse crowds of protesters, but neurological damage has never been documented in relation to the use of such strategies for public order management²⁰.

U.S. Embassy personnel who were victims of a hypothetical sound attack have been the subject of analysis by two medical teams with expertise in ear pathology and neurological damage assessment². Our study evaluated a review of the scientific literature, including descriptions of the case histories studied. Patient enrollment was not shared, and therefore data comparison is not meaningful. Each specialist team performed clinical evaluations and tests according to their own choice and not applying any shared study protocol.

In the scientific study directed by Dr. Randel Swanson, it is noted that: "If you took any of these patients and put them in a brain injury clinic, without knowing their background, you would think they had a traumatic brain injury caused by a car accident or an explosion in the military. It's like a concussion without a concussion." MRI examinations did not lead to an unambiguous and clear interpretation. They showed "nonspecific

white matter changes" which thus confirmed an unclear interpretation²¹.

Among the 21 patients evaluated with neuroimaging in MRI, (11 women, 10 men), there were 3 who reported nonspecific white matter changes, including 2 mild and 1 moderate².

For the evaluation of the case history, it is necessary to consider that symptoms such as reduced concentration and memory, confusional states, and sleep disorders, existed in almost all subjects²². Still, these symptoms are also frequently present in subjects with anxiety disorders, depression, or other psychiatric diagnoses. Commonly reported symptoms included visual disturbances, such as hypersensitivity to light, reading difficulties, and eye fatigue, but no visual impairment was found after a clinical examination²³. Impairment of convergence and eye tracking was observed in half of the patients, evidence that it is also common in anxious subjects. In addition, three-quarters of the subjects complained of headaches, half of which presented hypersensitivity to light and sound, classic symptoms of migraine, from which about 15% of the population is affected¹. Ear specialists, after examining 25 subjects from the U.S. Embassy staff, stated that all subjects reported injuries to the otolithic organs whose function is to regulate balance, perception of gravity, and movement. The study focused on 25 subjects who experienced symptoms after direct exposure to noise¹⁶. Ten subjects who were within a short distance of the subjects affected by the external sound were also evaluated. In none of these 10 subjects was identified an otolith lesion. Only a few reported, "an extremely brief sensation of exposure to a wave and a sharp noise for several seconds."

A vertigo syndrome was the most common diagnosis among the cases reviewed: dizziness (92%), followed by cognitive deficits, difficulty concentrating, brief amnesia, longer time to process information, and feeling "foggy" (56%), hearing loss (32%), ear pain (28%), and headaches (24%).

From the vestibular tests and eye movement evaluations, there was an alteration that could not be referred to a certain and clear diagnosis. From our perspectives, this conclusion was also justified by the absence of an adequate control group.

We also considered neuroimaging studies reported in the literature. One neuroanatomical feature assessed with brain MRI, which currently has no scientific explanation, is the finding of brain alterations as it occurs in cases of minor brain trauma that evidently did not occur in the subjects studied.

The alterations evidenced by MRI have been evaluated and criticized, especially for the lack of a control case study and for the absence of

adequate comparison between the symptoms reported by the subject and the MRI evidence¹⁶. The radiological studies were evaluated by a group of specialists from the University of Pennsylvania and investigators from Dalhousie University in Halifax, Nova Scotia. The first group found substantially normal structural magnetic resonance imaging (MRI) results, even though the neuroimaging process had been performed months or years after the initial symptoms². Some criticisms of the neuroimaging examinations performed have been confirmed in the literature. More specifically, it has been described that there were small differences in functional connectivity in auditory and visuospatial networks among the 40 Havana patients compared to 48 healthy controls. As described in the literature, difficulties in the replication of results are common in studies of small groups of patients using measurements and comparisons of images acquired with MRI²⁵. Neuroradiology specialists at the NIH (National Institute of Health) have performed imaging on a small number of the Havana court even at later periods, although unable to document features suggestive of a definite brain alteration. From the review of the scientific literature, we can therefore confirm that, in our opinion, no scientific studies that have considered an adequate number of patients have been published. In addition, the criteria for enrolling patients with a possible diagnosis of Havana Syndrome are not defined.

ETIOPATHOGENETIC HYPOTHESES

Among the first etiopathogenetic hypotheses, the possible target emission of harmful sounds has been considered. The hypothesis at the moment has not been confirmed in any way. In particular, exposure to audible sounds between 20 Hz and 20000 Hz does not appear to be causally related to lesions of the central or peripheral nervous system that could justify the reported symptoms²⁰.

In the report of the National Academies of Sciences, Engineering, Medicine, it has been hypothesized a relationship between signs and symptoms of acute type, with the possible presence of a direct radiofrequency on the subjects involved. The heterogeneity of the symptomatology has been justified by hypothesizing a relationship between the latter and the time of exposure. The different interpretations of vestibular symptoms evaluated by different specialists are also to be taken into account.

The same committee considered the possible exposure to chemicals, infectious diseases, and possible psychiatric diagnoses, considering in some cases a possible tendency to extension and possible crystallization of signs and symptoms².

Among the exogenous substances, exposures to organophosphates or pyrethroids used as insecticides in the territory of Havana were hypothesized¹⁷. No convincing evidence of a relationship between exposure to these substances and symptoms has ever been documented in the scientific literature.

Between 2016 and 2017, an infectious agent capable of causing neurological manifestations was present in Cuba. However, this epidemic, defined as Zika, could not justify in any way a relationship between the type of symptom onset and the possible infection. Still debated are the possible mechanisms of interference of other causal factors, such as psychological or social ones. With reference to subjects who presented chronic symptomatology, there was a consensus in identifying a diagnosis of "persistent perceptual postural vertigo" (PPPV). Signs and symptoms are, in fact, consistent with a functional disorder of the vestibule of non-psychiatric origin that can be triggered by a vestibular, or neurological defect, resulting in chronic symptoms. In addition to the PPPV hypothesis, a relationship between the administration of direct pulsed energy and the onset of symptoms was found to be plausible, especially in the first documented cases²⁶.

As described in the National Academies of Sciences, Engineering, and Medicine report signs and symptoms were documented as follows:

"Some of the acute signs and symptoms persisted or recurred and became chronic in some individuals, including dizziness (23 of 25 at the time they were examined in Miami and 13 of 21 in Penn), fatigue (10 of 21 in Penn), impaired balance (numbers not available), headaches (6 of 25 in Miami and 16 of 21 in Penn), impaired concentration (5 of 8 in Miami and 8 of 21 in Penn) and memory (5 of 8 in Miami and 11 of 21 in Penn), depression (numbers not available), and insomnia (18 of 21 in Penn)². These latter symptoms alone do not confirm a specific etiologic diagnosis and may be due to a wide variety of common disorders (including viral and other inflammatory conditions, persistent postural-perceptual dizziness, chronic fatigue syndrome, traumatic brain injury, post-traumatic stress disorder, depression, and others)."

Tests used to assess the vestibular system included the Dizziness Handicap Inventory and balance performance tests such as dynamic posturography. These surveys revealed high rates of impairment and reactivity. The scientific literature shows that medical professionals have interpreted these data as evidence of injury to the inner ear or to the cerebral cortex³.

Again, among the many limitations of the tests used is the possible interference of pre-existing functional or psychiatric anatomical alterations. These may appear alone or in combination. Therefore, the review confirms that these findings

indicate a high impairment of the vestibular apparatus at the time of testing without being able to identify any hypothesis regarding its cause.

Another consideration that should not be overlooked is that the use of tests must provide for adequate collaboration of the patient without the latter voluntarily interfering in the execution and the results.

With regard to instrumental investigations of the vestibule, it was concluded that in four groups studied in different locations, there was no way to ascertain a relationship between test results and a definite brain injury²⁵. However, one must consider the heterogeneity of the case studies examined. In fact, among the four groups of patients examined, there are differences in the time of execution of the tests: in some cases, they occurred at the beginning, and in other cases, in a chronic phase.

From a neuropsychological point of view, the tests did not provide comparable and standardizable results. The same committee (National Academies of Sciences, Engineering, Medicine) concluded that the tests used were not significant in being able to identify definite cognitive deficits.

Among the possible causes, mass psychogenic illness has been taken into consideration. This hypothesis, however, is not confirmed by any clinical evidence. A clinical feature in contrast to a mass psychogenic syndrome is the prolonged presence of signs and symptoms over time²⁷. The review reveals other hypotheses, such as an etiology of viral or chemical type (or both types). In our opinion, an 'absence of fever in the entire case history is not completely consistent with an infection of viral or another origin. Additionally, an injury derived from chemical intoxication is inconsistent with the absence of multiple organ involvement²⁸.

On the other hand, there is also no common consensus in the interpretation of neuroimaging studies regarding the so-called "brain injury without injury"²⁹.

Among the discordant features, we can mention the presence of unilateral otalgia and unilateral vestibulopathy: this symptomatology is at least partially discordant with even a minor traumatic brain event. Even the prognosis of a minor brain trauma is not consistent with the evolution (sometimes chronic) of a possible Havana Syndrome. Uncomplicated minor traumatic brain injury has a rapidly favorable prognosis, whereas, in Havana Syndrome, symptomatology has been documented to be sometimes persistent for months, with no demonstrated improvement, at least until adequate rehabilitation begins³⁰.

RECOMMENDATIONS

In this review, the authors evaluated the recommendations described in the National

Academies of Sciences, Engineering, and Medicine report. These recommendations are supportable in our view.

Non-scientific open sources are documenting a steady increase in the number of cases, confirming the involvement of geographically distant sites. The onset and the symptoms are still overlapping and unchanged compared to the first cases documented in Cuba¹.

Since the most recent episodes have not been included in any way in a systematic study, we believe that it is reasonable, from a clinical point of view, to implement a standard protocol of enrollment of the subjects involved.

First recommendation:

Create a coordinated specialist medical team that can evaluate the subject within 24 hours of the onset of the symptom.

This recommendation aims to avoid evaluations at a distance of time from the onset, which would be unfavorable to a rapid diagnostic framework that is essential for the standardization of data collection.

Second recommendation:

Establish a specialized medical scientific and technical working group for a definition of the protocol to be applied in a univocal and shared way for each case.

We believe that clinical and neuroradiological evaluations and tests should be codified in their application. This will allow to obtain valid data for the epidemiological study and, last but not least, for the identification of a possible cause and evolution.

To date, patients have been evaluated at different sites and with different diagnostic and investigative methods.

Third recommendation:

Definition of criteria for the enrollment of patients with typical symptoms for a possible Havana Syndrome.

Referring to the available scientific literature, and in particular to documented signs and symptoms, we believe we can propose criteria for inclusion or exclusion of patients reporting the onset of a possible Havana Syndrome.

The major criteria are defined with reference to the data collected in the study: Cuba Unexplained events investigation - Final Report, Havana, Cuba, August 2016 to March 2019 - Center for Disease Control and Prevention 12/03/2019.

We considered the documented cases of 95 patients potentially affected by Havana Syndrome.

However, given the small numbers, it is impossible to propose reliable statistical data.

From the literature, we know that the documented cases through 2019 are all referable to US or

Canadian federal or diplomatic offices in Cuba or to the fact that symptomatic individuals had returned from Cuba.

INCLUSION CRITERIA:

In order to define clear and precise criteria for the inclusion and enrollment of patients in a scientific study, it is necessary to overcome the different doctrinal approaches of the different schools. This is feasible only by addressing the problem of possible diagnosis on a purely descriptive and syndromic level that prescinds from preconceived theoretical positions. This approach, in spite of the limitations we have just mentioned, represents an overcoming of the traditional clinical diagnosis. Most of the clinical evaluations performed in the studies described in the literature have considerable margins of subjectivity, contributing heavily to the uncertainty of the clinical diagnostic judgment³¹.

A common way of collecting the required information will be essential, as well as an assessment of the quality of the information collected; the clinician, based on his or her experience, will need to be able to evaluate whether the patient has well understood the questions asked, whether he/she has answered truthfully or falsely, and whether he/she has in any way attempted to reinforce and make signs and symptoms credible. The clinician will need to ward off attempts to simulate illness, characteristics of chronicity, or symptoms extension. He or she will also need to pay attention to possible dissimulations that the patient might implement with the aim of maintaining his/her ability to work or his/her social status. It will be necessary to check whether the environmental situation or the doctor-patient relationship may have influenced the quality of the responses, whether the responses themselves are influenced by particular existential or emotional situations and more. From this last statement, it is possible to understand the high value of an adequate anamnestic collection aimed at identifying possible pre-existing organic or psychiatric pathologies.

In the last three years, the case history of possible subjects affected by Havana Syndrome has expanded to U.S. diplomatic offices outside Cuba, no longer confirming an exclusive relationship with the stay on Cuban territory. However, this aspect has been described only in open journalistic and non-scientific sources.

Therefore, we must make it clear from the outset that all subjects, in order to be included in clinical trials, must be employees of federal offices (or their relatives), even outside Cuban territory. For the definition of the criteria, we respected some clinical principles for the correct enrollment of patients.

Inclusion or eligibility criteria are likely to influence the study's power and its external validity (generalizability); they should be defined before the enrollment of participants and should be simple and unambiguous. Ideally, enrolled subjects should initially be considered to have the disease or clinical condition that is being investigated. Subjects who are found to be unaffected by the condition of interest or who are not at risk of the outcome of interest may not gain any benefit from enrollment in the scientific study. Failure to meet these criteria and the criteria of inclusion is likely to "dilute" the effectiveness of the study.

Overly restrictive inclusion criteria result in a very homogeneous sample, but this sample often compromises the trial's applicability.

In the study of the reports of possible Havana Syndrome, the use of initially broad and generic inclusion criteria has many advantages, in particular easy and rapid recruitment and less time in the screening phase of the patients.

Further care must be taken to include participants at very low risk of the outcome. In this case, there are some disadvantages: for the same effectiveness of the intervention, the power of the study is reduced; secondly, the increase in sample size with the consequent extension of the recruitment phase may extend the duration of the follow-up; in turn, this could reduce the possible effectiveness of the medical intervention to be implemented in prevention.

The primary goal of exclusion criteria is to minimize potential risks to participants, particularly by excluding those with a high probability of adverse events.

Also, attention should be paid to avoid including participants with a high probability of drop-out. The enrollment of patients who may drop out of the study or die before its completion from diseases unrelated to the inclusion criteria makes it difficult to ascertain the primary end-point in all participants.

To prevent drop-outs, we considered some features: define specific exclusion criteria for these participants, ultimately improving the statistical efficiency of the trial; evaluate from the beginning the potential compliance by providing a run-in phase before the randomization of participants.

It must be considered that both strategies increase the trial's internal validity but reduce its generalizability.

Given the geographic spread of cases of possible Havana Syndrome, we must consider an applicable care setting in different geographic areas. The care setting (hospital and specialist care in University centers) and the geographical area of enrollment affect the prevalence/incidence of certain diseases/conditions, the characteristics of the

patients included, and the prevalence of the outcome of interest, to the point of making the results of the study inapplicable in different contexts.

Classification of exclusion criteria with respect to enrollment of subjects with possible Havana Syndrome.

Strongly justified

- - Inability to provide informed consent
- - Not being US federal employees or their relatives
- - Risk of intervention or placebo:
 - Unacceptable risk of adverse reactions to diagnostic procedures.
 - Unacceptable risk of participant assignment to placebo and/or discontinuation of active treatment for other pre-existing conditions
- Difficulty in interpreting the effectiveness of the intervention:
 - The individual is taking another treatment that may confound the efficacy of the one under study
 - The individual has an independent condition with signs-symptoms similar to those of the condition of interest that make it difficult to assess treatment effects

Potentially justified

- Potentially limited compliance
- Possible non-completion of follow up

Adapted by Van Spall HG, et al. JAMA 2007

Given the above, we identified inclusion criteria. The criteria defined below are derived from a nonstatistical study because of the limited number of patients described in the literature. Once a sufficient number of patients have been enrolled in systematic studies, it will be possible to define a more precise list of criteria for inclusion and possibly for diagnostic purposes. Hopefully these criteria will be universally recognized for the diagnosis of Havana Syndrome as well.

Major inclusion criteria (at least three criteria must be present):

- Sudden auditory symptoms
- Acute onset with headache
- Nausea
- Sensation of "head pressure"

- Vestibular disturbances

Minor criteria:

- Biphasic-like onset
- Spatial time disorientation
- Late onset of cognitive deficits
- Vision deficits

To include subjects with symptoms in a systematic study, the subjects will need to present four major and two minor criteria, or three major and three minor criteria.

LIMITATIONS

The review of the literature shows that the study of the results obtained from the diagnostic activities performed was limited mainly because of the impossibility of comparing the data collected. Obviously, we are aware that the need to maintain adequate confidentiality regarding the case histories must also be considered in view of the fact that they involved federal employees. With regard to the case history, which in some cases involved the relatives of the employees, there was an even greater difficulty in finding clinical information regarding the evolution over time.

The finding of acute, biphasic and chronic symptomatology has made the population to be subjected to specialized medical assessment and adequate follow-up even more heterogeneous. In all the scientific articles we examined, details regarding the precise geographical location were omitted. Another limitation is given by the presence of clinical and instrumental evaluations initially not complete, not coordinated, and performed at different times, sometimes very distant from the onset.

In our opinion, a number of cases have probably escaped observation as suffering only from mild symptoms, which do not require medical intervention.

Having no certainty about the etiopathogenesis of these symptoms, it was not possible to understand why some subjects developed an acute or biphasic onset disease and others a chronic one. In particular, some patients may have been reported or interviewed two or more times, resulting in an alteration of the overall data. Patients were evaluated and described at different times, also considering signs and symptoms that appeared sometime after a possible Havana syndrome. In addition, behavioral aspects, such as a possible tendency for symptoms to extend and become chronic or a possible dissimulation of symptoms, were not clarified.

The absence of inclusion criteria to share the enrollment and study of patients remains the major limitation.

CONCLUSIONS

The authors, through a review of the scientific literature, identified clinical signs and symptoms of US federal employees and their relatives who had an onset of possible Havana syndrome.

We believe it is important to identify a common strategy to enroll patients and study them through a shared methodology. The enrollment of patients, in accordance with the defined criteria, allows the collection and evaluation of clinical data, instrumental and radiological investigations, and possible tests.

Only by sharing these clinical data will it be possible to define any future diagnostic criteria with greater clarity. It will also facilitate this clinical phenomenon's rehabilitation, treatment, and epidemiological evaluation. The correct enrollment of patients in a clinical study will allow

us to clarify as much as possible the etiopathogenetic hypothesis. Such information will also be useful for studies by specialists, technicians, intelligence, and engineers involved in the evaluation of possible external causes.

Declarations:

Ethical Approval

Not applicable

Competing interests

The authors declare that they have no competing interests

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Availability of data and materials

The data used for this study can be found on PubMed (<https://pubmed.ncbi.nlm.nih.gov>).

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