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UNDERSTANDING ALIEN LIMB SYNDROME: AN INTERDISCIPLINARY REVIEW OF NEURAL MECHANISMS AND CLINICAL FEATURES

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ABSTRACT

Research objectives: Alien limb syndrome (ALS) can be described as complex, autonomous limb movements that occur against the patient's will. The aim of this study is to summarise the current state of knowledge about alien limb syndrome.
Methods: Literature in English was reviewed via PubMed and Google Scholar. After analyzing the abstracts, 30 publications closely related to the topic, 77% of them published between 2017 and 2024, were selected.
Key findings: The etiology of alien limb syndrome remains poorly understood. There are several phenotypes of ALS associated with different sites of damage to brain structures: the frontal and callosal phenotypes, which may also be called anterior, and the posterior phenotype. Possible symptoms include: inter-manual conflict, mirror movements, grasping, utilization behaviour, hemineglect, hemianesthesia, ataxia. Alien limb syndrome usually occurs in association with damage to brain structures caused by tumors, vascular events or postoperative injuries and in people with corticobasal syndrome, Creutzfeldt-Jakob disease or Alzheimer's disease. No specific therapeutic regimen has yet been identified. Sometimes behavioral therapy has been effective in patients and some use pharmacological treatment, including botulinum toxin.
Conclusions: Alien limb syndrome is a relatively rare phenomenon. It is not a fully understood disease entity. Further research is needed to better determine the etiological factors and thus develop an appropriate therapeutic approach and be able to better care for patients.

KEYWORDS

Alien Limb Syndrome, Alien Limb Phenomenon, Brain Lesions, Motor Dysfunction, Disinhibition

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1. Introduction:

Alien limb syndrome (ALS) was first described in 1907 by Van Vleuten, who observed it in a patient with right-hand grasping who had a left cerebral hemisphere tumor infiltrating the corpus callosum. [1] A year later in 1908, Kurt Goldstein identified it in a woman after a stroke who claimed to feel that someone else was using her hand. Woman tried to strangle herself with her left hand against her will. In 1972, Brion and Jedinak used the name "the strange hand" to name the phenomenon, and the word "alien" limb was introduced into the nomenclature in 1979 by Bogen. The first attempt to describe the phenomenon was undertaken by Della Sala in 1991. [2][3][4]

Our sense of ownership over our bodies is a complicated and multidimensional process. In ALS, it is most likely disrupted. [5] Alien limb syndrome can primarily be described as unintentional, unwanted, simple or complex movements. These may appear to be desired by the person, but are performed against the patient's will. [6] Some patients described these movements as "aggressive" and even denied having the limb due to the very strong feeling of alienation. [7] However, it is important to distinguish ALS from the anarchic limb phenomenon, in which involuntary movements appear, although directed towards a specific goal. [8] When volitional control is disturbed, there is a feeling of lack of control over one's own limb and the sensation of some external force acting on it. [4] The movements that occur in people with ALS can be divided into two groups: complex motor acts and simple, quasi-reflex movements. The former include intermanual conflict or mirror movements, while the latter include reaching, grasping and levitating the limb. [9]

2. Materials and methods:

A collective literature review was conducted using well-established medical research databases, such as PubMed and Google Scholar searching for data on alien limb syndrome. After analysis of the abstracts, 30 of the 110 found articles that were closely related to the topic of the paper were included. The included studies were published between 2010 and 2024, were in English, conducted on humans and contained data on alien limb syndrome.

3. Epidemiology:

There are currently no data describing the frequency or mortality of alien limb syndrome. It is a relatively rare condition, mainly associated with brain damage. [4] However, the incidence of ALS is estimated to be relatively low. [10] One study conducted on 150 patients showed that alien hand syndrome affects women and men almost equally and that the median age is 64 years. [11]

4. Etiology:

The etiology of alien limb syndrome remains poorly understood. The most common cause is damage to the frontal lobes, which are responsible for executive functions and voluntary movements. This causes one limb to perform involuntary movements while the other is under voluntary control, which is caused by a disruption in communication between the hemispheres of the brain. [4] It is said that the mechanism of its development consists of brain disinhibition. Despite analyzing many cases, it has not been possible to precisely describe the cause of the syndrome. One article indicates that alien hand syndrome is a disorder of 'predictive processing' in hierarchical sensorimotor brain networks. There is a disruption of input from medial areas, primarily the supplementary motor area (SMA), where there is a modulation of the precision of lateral brain areas that encode anticipated action outcomes. One theory that accounts for disinhibition in the alien limb syndrome is that there is a continuous interaction between two functionally distinct premotor systems: lateral and medial. The lateral one provides an impulse to react to clear, external stimuli, which is partly dependent on motivational signals or the context of the performed activity. The middle one is responsible for performing movements, the signal to perform of which comes from within. Both of these systems should be closely connected and properly balanced. There are also "automatic" movements, which a person performs on the basis of old stimulus-response associations. Disinhibition of the lateral premotor system caused by damage to the medial system results in inappropriate ‘stereotypical’ actions, i.e. the appearance of alien limb syndrome. [6] Another theory proposes that frontal-parietal connections play a major role in determining potential voluntary actions. External stimuli activate representations of potential actions, described by Gibson (1979) as “affordances” that is characteristics of environmental items that encourage an observer to take action. ALS may be caused by exaggerated affordance or insufficient suppression of affordances. [6][12]

In various scientific sources we can also find information on Bayesian brain theories, which claim that the brain strives to maximize evidence for a “generative model” of the environment, so that previously acquired beliefs about it are consistent with observed sensory evidence. The effectiveness of the brain in regulating its environment depends on it creating a good model of it. Therefore, the brain will not be able to effectively regulate its environment if it holds aberrant prior beliefs. This will result in the creation of false inferences and maladaptive behaviour. Another study showed that contralateral involuntary movements were induced by stimulation of supplementary motor area. The occasional intention or "urge" to move a part of the body may occur after low-intensity stimulation of the SMA. Whether the movement performed in alien limb syndrome is simple or complex and how much it looks like a purposeful movement is primarily influenced by the location of the lesion. If posterior regions are damaged, primary, stereotyped movements will appear on hierarchical predictive networks. In turn, with damage to the anterior regions, the movements performed will be more purposeful and complex. In the case of frequent damage to the SMA in alien limb syndrome, intermediate level predictions will dominate in the movements performed by patients. The fact that in ALS the movements are usually short and simple is explained by the fact that the more direct predictions at a higher level dominate over longer-lasting ones. [6]

The authors of the articles state that ALS affects the left arm much more often. [13] Damage to the corpus callosum, according to Caixeta and colleagues, affects the nondominant hand (e.g., intermanual conflict). On the other hand, injury to the frontal lobe impacts the dominant hand (e.g., grip reflex). [14] The most commonly affected brain areas are the prefrontal cortex, supplementary motor cortex, anterior cingulate cortex, thalamus and corpus callosum, causing motor and sensory disturbances. [4] ALS can also be caused by damage to the network localized in the precuneus, which causes disordered agency. [15] Alien limb syndrome usually appears in connection with damage to brain structures caused by tumors, vascular events or post-operative injuries. [4] The occurrence of alien limb is associated with strokes - most often in the anterior or posterior cerebral artery. [16] It also occurs in individuals with corticobasal syndrome, Creutzfeldt-Jakob disease and Alzheimer's disease. Demyelinating disease, progressive multifocal leukoencephalopathy, hereditary diffuse leukoencephalopathy with spheres, posterior reversible encephalopathy syndrome, commissural transection, thalamic dementia, intracerebral hemorrhage and thalamic dementia are also possibly associated. [2] People with this condition may not be aware of their actions, which is why they may react to

them with a whole range of emotions – from laughter to frustration. There are also other diseases in which volitional control disorders appear – these include tics, choreographic movements or xenomelia. [6]

Risk factors for the occurrence of alien limb syndrome have not been identified yet. [17] The most common comorbidities with ALS include type 2 diabetes, hypertension, coronary artery disease, dyslipidemia, arrhythmias and obesity. [4] In one of the patients, the symptoms worsened when he had divided attention between concurrent activities, was stressed or tired. [18]

5. Imaging tests:

Neuroimaging studies have shown a lack of activity of the frontal lobe in ALS patients performing motor activities, and it should be remembered that it is usually active during planning and initiating movement. When there is a lack of preparatory activity of the frontal lobe, autonomic movements are initiated by the primary motor cortex. [4] Activated during alien movements, but not during voluntary movements, is the right inferior frontal gyrus, which shows inhibitory control of motor responses. [19] It has also been shown that changes in the pre-supplementary motor area and its connections are responsible for, among other things, the severity of symptoms. The medial frontal lobe and the anterior corpus callosum also played a very important role. However, despite many studies, the main cause of the appearance of alien limb syndome has not yet been revealed. [6] MRI showed that during finger twisting and rotation of the dystonic hand, there was isolated activation of the primary motor cortex, which was significantly higher on the affected side. This can be explained by impaired inhibitory control in this area caused by asymmetric atrophy. However, there is no precise MRI data linking involuntary and unconscious movements with the activation of specific cortical or subcortical areas. Several studies have found that the same brain areas are activated during both involuntary and voluntary movements. [20]

6. Phenotypes:

Symptoms occur primarily in the upper limbs, although there have been reports of lower limb symptoms. However, they are even more frequently misdiagnosed than those in the upper limbs, e.g. as myelopathy or radiculopathy, due to their rarity. [21]

There are several phenotypes of alien limb syndrome associated with different sites of damage to brain structures. [2] We have the frontal and callosal phenotypes, which can also be called anterior, and the posterior phenotype. [3]

In corticobasal syndrome, Creutzfeldt-Jakob disease and stroke, the posterior phenotype is said to be the most common. A whole range of symptoms appears here: apraxia, rigidity, neglect, self-agnosia, sensory disorders of the cerebral cortex and visible aloofness from the limb. The posterior phenotype occurs primarily in people with damage to the posterior part of the parietal lobes and the occipital lobe or thalamus. Symptoms may include involuntary lifting of the arm, uncoordinated movements of the hand and above all the feeling that the patient's hand does not belong to him. [2][22]

In the anterior phenotype, the most common reflex was the grasping reflex. Patients also had problems "releasing" objects or impulsively groping them. In this phenotype, the most common damage is to the medial prefrontal cortex or the supplementary motor cortex. Damage to the corpus callosum is also often mentioned. The most common cause is a stroke of the anterior communicating artery. The articles also state that symptoms more often appear in the dominant hand of patients. [2][23]

Additionally, we have a callosal phenotype that is frequently linked to apraxia. [24] When the corpus callosum is damaged, symptoms of disinhibition appear. Characteristically, the activity of the uninvolved hand is also affected due to the "disconnection" of both hands. However, there are no frontal symptoms or weakness, but there is alexia, anomia, visual or tactile anomia or apraxia. One of the causes is callosal demyelination or callosal infarct. [2] This is the most difficult ALS phenotype to diagnose, mainly because it is rare and often occurs together with other brain lesions. [4]

Table 1. Alien limb syndrome phenotype an its clinical features [3][4]

Alien limb phenotype	Clinical features
Frontal	Groping Grasping Utilization behaviour
Callosal	Inter-manual conflict Autocriticism Ideomotor dyspraxia Mirror movements
Posterior	Hemianopia Hemineglect Hemianesthesia Ataxia (moderate-severe) Hemiasomatognosia

There are also cases where patients show symptoms characteristic of all variants of alien limb syndrome. [3] One example would be a patient who exhibited features of both the callosal phenotype (intermanual conflict) and the posterior phenotype (hemianesthesia). [25] This is not a fully understood phenomenon, therefore it can be suspected that there are many more phenotypes of the disease that have not yet been identified. [2]

Another division of ALS was described by Pannikkath et al. They distinguished: alien hand sign, which is the feeling by the patient that his hand does not belong to him, diagnostic dyspraxia, defined as performing actions with one hand that are contrary to the other, and anarchic hand, which happens when the affected side performs goal-directed activity against the will of the person. They also indicate supernumerary hand, which is the feeling in the patient as if he had an extra limb. [14]

Fisher divided the symptoms of ALS into two groups: those involving utilization behavior (grasping, groping) and those involving complex, unwanted movements (inter-manual conflict, interference, mirror movements). [26]

7. Corticobasal syndrome:

Corticobasal syndrome (CBS) can be described as a clinical syndrome with very heterogeneous presentations. CBS includes dystonia or myoclonus, asymmetric limb stiffness, apraxia of speech, sensory deficits and alien limb syndrome. [27] It is a neurodegenerative disease leading to functional deterioration, with a typically asymmetric presentation of symptoms. [28] Cortical-basal degeneration, associated with aggregation of hyperphosphorylated 4-repeat tau protein, leads to the occurrence of cortical-basal syndrome. Other neuropathologies can also lead to its occurrence - e.g. Creutzfeldt-Jakob disease or Alzheimer-type pathology. In the case of cortical-basal syndrome, ALS is often present and is included in the international diagnostic criteria of CBS. The study showed that the occurrence of severe apraxia has no predictive value regarding the occurrence of ALS in the cortical-basal syndrome. [9]

8. Differentiation:

Alien limb syndrome must be distinguished from purely motor disorders, such as dystonia, grasp reflex, athetosis, hemiballismus, hemiataxia and utilisation behaviour, as well as from sensory neglect syndromes. [9] ALS should also be differentiated from psychiatric disorders with which it is often confused. These include: delusional disorders (infestation delusions, somatic delusions, Schneiderian delusions, xenomelia, somatic paraphrenia), body schema disorders (shape distortions, malfunction of limb, limb distortions, displacement of limb), movement disorders (choreiform movements, atypical Parkinsonism, tics) or depersonalization, schizophrenia and psychogenic dystonia. [4]

9. Treatment:

No specific therapeutic regimen has been identified to date. Sometimes behavioral therapy has been effective in patients. As with any condition, treatment should be tailored to the individual needs of the patient. Often, the patient is asked to perform an activity that usually triggers the appearance of unwanted movements in order to develop appropriate strategies for dealing with them. Then the patient trains using previously planned movement structures and planned strategies, after previously inducing alien limb syndrome. Due to the occurrence of damage in various structures, therapeutic methods should be adapted to them. In the case of

anterior ALS, cognitive behavioral therapy, sensory tricks and distracting tasks are mainly used. In posterior alien limb syndrome, pharmacological treatment (clonazepam or botulinum toxin A), visualization strategies and spatial recognition tasks are used. The main therapeutic approach in callosal phenotype is mirror box therapy. [3][4] In one patient, amantadine treatment resulted in moderate improvement in ALS symptoms. [29]

10.Prognosis:

Studies have shown that the prognosis of ALS secondary to neurodegenerative diseases is worse than ALS secondary to stroke. Symptoms may occur for several days or months, or even last for several years, but in about 68% of patients they decrease within a year of their first appearance. [4][30]

11.Conclusions:

Alien limb syndrome is a rare neurological condition. Diagnosis is often a challenge due to various types of brain damage and misinterpretation as one of the psychiatric disorders. The etiology of ALS is complex and the symptoms are very diverse. After appropriate treatment, both pharmacological and psychological, as well as support from rehabilitation specialists, the prognosis for sick patients is generally good. However, further research is needed to fully understand alien limb syndrome and thus develop appropriate therapeutic strategies and provide patients with appropriate care.

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