Alien hand syndrome: Pathophysiology, semiology and differential diagnosis with psychiatric disorders (Review)

MIHNEA COSTIN MANEA[1,2*], FLORIS PETRU ILIUTA[1,2*], MIRELA MANEA[1,2*], RADU MIHAIL LACAU[1], CORINA-IOANA VARLAM[1], ALISS MADALINA MARES[1], CONSTANTIN ALEXANDRU CIOBANU[3] and ADELA MAGDALENA CIOBANU[1,4]

[1]Department of Psychiatry, 'Prof. Dr Alexandru Obregia' Clinical Hospital of Psychiatry, 041914 Bucharest; [2]Department of Psychiatry and Psychology, Discipline of Psychiatry, Faculty of Dental Medicine; [3]'Carol Davila' University of Medicine and Pharmacy; [4]Neurosciences Department, Discipline of Psychiatry, Faculty of Medicine, 'Carol Davila' University of Medicine and Pharmacy, 020021 Bucharest, Romania

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Abstract. Alien hand syndrome (AHS) is an uncommon neurological condition characterized by involuntary, yet seemingly purposeful, movements of a limb, typically an upper extremity, with variable awareness and control by the affected individual. It is associated with a range of peculiar sensations, such as the feeling of limb estrangement, alien control and involuntary mirroring or restraining of movements. AHS indicates a profound disruption in volitional motor control and personal agency. The aetiology of AHS is the dysfunction of critical brain regions secondary to diverse neurological insults, such as tumours, vascular disorders, infarction or neurodegenerative diseases. It is clinically categorized into the parietal and callosal types, depending on the affected region, with manifestations often linked to the specific brain region affected. The callosal type is particularly challenging to diagnose due to its rarity and potential for nonspecific or concealed symptoms amid concurrent brain injuries. Distinguishing AHS from psychiatric disorders is crucial for accurate diagnosis and improved patient outcomes. Further research is imperative for a deeper understanding of the pathophysiology of AHS and the development of effective treatments. AHS predominantly affects adults and is frequently associated with multiple comorbidities. The syndrome is also exemplified by three distinct motor behaviours: Involuntary grasping, inter-manual conflict and limb levitation accompanied by the sensation of an alien limb or the perception of external control over one's movements. It has a generally good prognosis with partial or total recovery following appropriate rehabilitation techniques, including pharmacological and psychological measures.

Correspondence to: Dr Floris Petru Iliuta, Department of Psychiatry, 'Prof. Dr Alexandru Obregia' Clinical Hospital of Psychiatry, Str. Berceni 10-12, 041914 Bucharest, Romania
E-mail: floris.iliuta@umfcd.ro

*Contributed equally

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Contents

1. Introduction

Alien hand syndrome (AHS) is a rare neurological disorder characterized by involuntary, yet seemingly purposeful, limb movement, with partial or absent awareness. In 1908, Goldstein first described AHS in a case where a woman's left hand acted against her will, attempting to strangle her (1,2). Given the rarity of the syndrome, no data on the prevalence or mortality rates are available. This syndrome is often linked to cerebral lesions, particularly strokes that affect the right hemisphere of the brain and the corpus callosum, the connecting neural bridge between hemispheres crucial for integrating and relaying information across the hemispheres (3).

The syndrome primarily involves damage or injury to the frontal lobes of the brain, which are crucial for voluntary movements and executive functions, and manifests as a disconnection syndrome. Damage in these regions disrupts the harmonious communication between hemispheres, resulting in one hand operating under voluntary control and the other exerting involuntary movements (4). Theories regarding AHS suggest that a malfunction in the medial premotor cortex, which is responsible for internally guided movements, could lead to the disinhibition of the lateral premotor cortex, thereby causing involuntary motor actions. In addition, impairment in the frontal-parietal neural network, responsible for selecting voluntary motor actions, may also contribute to the development of AHS (5).

Neuroimaging advances, particularly functional magnetic resonance imaging, have illuminated the neural underpinnings of AHS, showing that, during motor tasks in patients with AHS, the frontal lobe, which is ordinarily active in the planning and initiation of movement, remains inactive. Instead, the primary motor cortex appears to initiate autonomous movements, without the typical preparatory activity of the frontal lobe (6,7). This lack of frontal lobe engagement indicates a bypassing of the normal motor planning processes, resulting in autonomous activity of the affected limb. Such neuroimaging findings provide critical insight into the disjunction between the intention of moving and actual motor execution that characterizes AHS, enhancing our understanding of this complex syndrome. Further development and wider-scale availability of adequate brain imaging techniques with emphasis on the functional aspects are crucial for creating personalized treatment and rehabilitation strategies.

The main focus of this review is the exploration of a rare and insufficiently researched neurological condition, which can be easily misdiagnosed or misinterpreted as a psychiatric disorder.

2. Search strategy

A collective literature review from January 2023 to January 2024 was conducted using well-established medical research databases, such as PubMed, Google Scholar, Science Direct, Elsevier, Springer Link and Medscape, searching for data on AHS and psychiatric disorders. The following search terms were used: 'alien hand syndrome', 'psychiatric disorders', 'psychiatric symptoms', 'differential diagnosis', 'depression', 'affective disorders' and 'psychosis', in various combinations. The included studies were published between 2000 and 2023, were in English, conducted on humans, included patients aged 18 years or over, and contained data on psychiatric disorders and diseases with symptoms similar to those of AHS, as well as psychological insight about rehabilitation. Studies that strictly focused on neurological or imagistic aspects of AHS, or had no connection to the field of psychiatry or psychology, were excluded. Limitations of our search strategy include publication, language and database bias, grey literature, incomplete retrieval of identified research, search term and timeframe bias, scarcity of available data (next to no findings from the last three years on the subject) as well as impact factor of different medical journals. The lack of data regarding specific laboratory testing or other medical investigation techniques could represent a potential limitation. Also, given the modesty of the available sources, no quality assessment of the retrieved data was performed.

The present study highlighted the marked associations between psychiatric symptoms, and morphological and pathophysiological substrates, and provided further insight for the adequate and integrative management of medical conditions.

3. Review

Classification, aetiology and clinical presentations. AHS exhibits a wide spectrum of clinical and behavioral manifestations, with certain patients maintaining awareness of their involuntary actions and others remaining oblivious to their abnormal motor activities until it is brought to their attention. Emotional responses to these involuntary movements vary, ranging from embarrassment and anger to shock and laughter (8). A notable case involved a woman with AHS who experienced involuntary control of her affected hand while eating and during social interactions, causing significant emotional distress (9). Another relevant case was reported in 2023 and involved a 72-year-old woman with a frontal variant of AHS determined by infarction in the anterior cerebral artery; the patient was aware of her hand moving involuntarily and learned to consciously restrain her right hand's autonomous movements using psychological rehabilitation techniques (10).

The pathogenesis of AHS is linked to cerebral insults, such as post-surgical trauma, neoplasms, vascular events and neurodegenerative conditions. Common comorbidities include hypertension, coronary artery disease, type 2 diabetes, dyslipidemia, cardiac arrhythmias, obesity and chronic smoking (11).

Affected cerebral regions often include the anterior prefrontal cortex, posterior parietal cortex, supplementary motor area, anterior cingulate gyrus, thalamus and corpus callosum, resulting in both motor and sensory disturbances. Motor symptoms may present as agnostic dyspraxia, which in right-handed individuals may manifest as the left hand performing contradictory actions. Sensory symptoms may include the sensation of the hand being foreign or the perception of additional limbs (12).

AHS can be indicative of a disrupted body schema-a dynamic, multisensory representation of one's body that allows for seamless interaction with the environment, thought to be mediated by the frontal-parietal network (13,14).

AHS has been classified into the frontal and callosal subtypes. The frontal subtype is a result of damage to the medial prefrontal cortex and is characterized by involuntary grasping and groping, while the callosal subtype, which is associated with corpus callosum damage, manifests primarily as inter-manual conflict (Table I) (15,16).

In particular, the right cerebral hemisphere is more commonly implicated, with injuries to the right parietal cortex leading to motor and sensory unawareness (17).

Injuries to the frontal lobe, particularly in the cingulate gyrus and supplementary motor area, have been linked to uncontrolled motor actions due to a disruption in inhibitory control (18). Furthermore, comprehensive neuroimaging is crucial for diagnosis, as AHS can be accompanied by a range of neurological symptoms (19,20). Callosal AHS is relatively rare due to the robust vasculature of the corpus callosum; however, when it occurs, it often coexists with other cerebral insults, rendering diagnosis challenging (21).

AHS also manifests in neurodegenerative diseases such as cortical-basal ganglionic degeneration and Alzheimer's disease, often presenting with ideomotor apraxia and limb rigidity (22,23). Corticobasal syndrome, which may lead to AHS, is characterized by motor dysfunctions and is often secondary to various neurodegenerative disorders (1,24).

Differential diagnosis with psychiatric disorders. The symptomatology of AHS requires differentiation from psychiatric disorders, which tends to be challenging (25). AHS may be easily mistaken for one of the following psychiatric disorders,

Table I. Association between clinical manifestations and injury localization.

Alien hand type	Damaged cerebral area	Clinical manifestations
Frontal	Supplementary motor area	Groping
	Cingulate gyrus	Grasping
Callosal	Corpus callosum	• Inter-manual conflict (non-dominant hand)
		• Autocriticism (the patient's reaction to the alien hand behaviour)

Information from Brainin *et al* (17).

Table II. Differential diagnosis.

Disorders	Manifestations	(Refs.)
Delusional disorders/beliefs	• Alien limb	(25-27)
	• Loss of identity of a body part	
	• Attributing the limb to someone else	
	• Separation of a limb	
	• Infestation delusions	
	• Somatic delusions	
	• Schneiderian delusions	
	• Xenomelia	
	• Somatic paraphrenia	
Body schema disorders	• Limb distortions	(25)
	• Shape distortions	
	• Displacement/absence of limb	
	• Malfunction of limb	
	• Xenomelia (body integrity dysphoria)	
Movement disorders	• Atypical Parkinsonism	(28,29)
	• Choreiform movements	
	• Tics	
Other psychiatric disorders	• Schizophrenia	(30)
	• Depersonalization	(31)
	• Psychogenic dystonia	(1)

particularly if medical professionals are unfamiliar with its clinical presentation (Table II).

i. Psychogenic dystonia, which has variable presentations, often accompanied by pain, weakness, responsiveness to psychotherapy, suggestion or placebo, and manifests as multiple somatizations or 'evident' psychiatric disturbances.

ii. Complete anaesthesia or deafferentation of a limb may lead to denial in its possessor and represents a form of somatic paraphrenia. In this case, dispossession is accompanied by delusional beliefs, such as personification of the involved limb or attribution of the limb to someone else (26). Patients with AHS are often under the impression that the involved limb behaves as if it were under the command of another individual. Such statements may sound like depersonalization or that the involved hand assumes a completely different 'personality' (27).

iii. Somatic delusions and attentional disturbances should also be taken into consideration (28). The somatic subtype of delusional disorders has been presented as a monosymptomatic hypochondriacal psychosis. The most common symptoms of somatic delusions are those regarding infestation (such as parasitosis).

iv. Distortion of the body schema, including distortions of the limbs, such as shape-related distortions or displacement, absence or malfunction, are also common.

v. Symptoms such as body pain and weakness, or loss of identity in a body part accompanied by a sensation of separation or alien limb also constitute somatic delusions (29).

vi. Patients with depersonalization disorder typically complain about emotional detachment, but depersonalization-derealization disorder can also be experienced as a feeling of detachment from own feelings or experiences, where objects, people and surroundings can seem unfamiliar, distant, false and lifeless (30,31).

In order for a limb to be described as alien (anarchic), its volitional control has to be severely affected and diminished. The feeling of losing control of one's own limb is accompanied

by the sense of external control of that limb, but the patient's sense of agency for other actions is maintained. Symptoms observed in AHS are not associated with and should not be mistaken for Schneiderian delusions of passivity and external control (32).

Other clinical disorders with abnormalities of volitional control that are nonetheless different from alien limb syndrome have been reported (32):

i. Psychogenic movement disorders can incorporate movements that are recognized as involuntary, without having a neuropathological organic substrate. In general, they are classified as stereotyped movements (33).

ii. Tics are also considered involuntary movements or vocalizations which are relatively out of one's control. Tics are idiomatic expressions, which can be partially and temporarily inhibited with mental attempt or by focusing on other activities (33).

iii. Choreiform movements and disorders are a continual succession of involuntary, brief, transient, migratory muscle contractions (34). Compared with the manifestations of the alien limb, choreiform movements are individualistic and are not influenced by environmental suggestion.

iv. Xenomelia is a rare syndrome in which patients feel that one or more limbs do not belong to them. At times, a desire for amputation can co-occur with the syndrome (35).

v. Dystonia and arm levitation. Each of them occurs without modification of self-perception and both can be seen in atypical parkinsonism syndromes, such as progressive supranuclear palsy and pure limb apraxia. These syndromes can be easily differentiated by the absence of involuntary movements. When uncommon limb movements are present, particularly when only one limb is affected, imaging is important to identify the underlying structural lesions, such as tumours, stroke or cerebral atrophy caused by neurodegenerative diseases (36).

A previous study described AHS as ego-dystonic, a psychiatric term that describes a set of thoughts, feelings or behaviours as inconsistent and incompatible with the patient's total personality. This is contrary to the term ego-syntonic, in which one's thoughts, feelings and behaviours are admissible, acceptable and consistent with the individual's total personality (35).

At times, radical decisions need to be made, particularly when the involuntary movements of the patients can threaten their own safety. In a case report about a patient diagnosed with AHS, the placement of physical restraints was needed due to excessive and uncontrolled exploration of the patient's own face and surrounding objects in an involuntary manner (36).

Psychiatric symptoms associated with conditions that affect the brain can also be included in the differential diagnosis (37,38).

AHS may be evidentiated by specific types of experiments and procedures, such as the alien hand experiment and the mirror box procedure.

Experiments and procedures

The rubber hand illusion. The alien hand experiment was developed by Torsten Ingemann Nielsen in the 1960s for the purpose of evaluating volition and intention in humans. Other studies using similar experiments have since been conducted to compare how normal individuals and patients with schizophrenia assess different movements as their own or performed by others (39).

For the classic rubber hand illusion, the participant is seated on a chair in front of a table, with their hands placed on it. A standing cover is used to mask the left or right arm from the patient's view. Next, an experimenter places down a real-life sized rubber hand of a left or right hand on the top of the table, in the same manner as the patient's real hand. Next, the experimenter uses two small soft brushes to touch both the rubber hand and the subject's hidden hand in concomitance or in asynchrony. Approximately 80% of subjects develop a sense of ownership of the rubber hand (40).

Self-hand recognition task. This task was performed in a previous study as follows. Gray-scale pictures of left and right hands were presented on a computer screen. The pictures were real photos of hands taken with a digital camera. Two stacks of pictures were presented one after another. In a random order, one stack of pictures presented left hands only and the other right hands only. In each stack, pictures containing the participant's own and other people's hands were introduced. All patients with AHS showed unimpaired performance as compared to the controls when asked to identify their right and left hands, demonstrating the same level of accuracy in acknowledging their own hand as the control subjects (41).

Body schema task. The mechanism behind this task relies on the multisensory capacity of our brain and body, where proprioceptive information regarding one's own body may affect the visual perception of others' body positions as well. In a previous study where this task was performed, patients with AHS did not recognize any difference between the postural changes of the models during the experiment (41).

Mirror box procedure. The mirror box procedure (mirror box training) is a procedure where participants observe the reflection of their unaffected hand, mimicking the movements of it with their affected hand, which is hidden behind a mirror. This experiment allows us to appreciate both the contribution of sense of ownership and sense of agency to the embodiment of an alien hand by controlling the parallelism between motor command and visual feedback. There is also a mirror box therapy for AHS used as a rehabilitation type of treatment (42).

A case study suggested an improvement in performance while seeing the reflection of the unaffected hand movement in the mirror (43). This type of experiment must be differentiated from AHS, in which patients are affected by brain lesions and their motor actions are involuntary for the affected hand.

Treatment. When it comes to the treatment of AHS, the available literature has documented no specific or targeted treatment. There are two options that need to be considered. Both pharmacological and behavioural interventions have been shown to improve the quality of life of patients with AHS. The treatment of choice should be selected according to the type of lesion that caused the AHS (Table III). The therapeutic methods for anterior AHS include sensory tricks, distracting tasks and cognitive behavioural therapy for anxiety control, but in the case of posterior AHS, more appropriate methods could be visualization strategies, spatial recognition tasks and pharmacologic treatment with botulinum toxin A and clonazepam (44).

Table III. Therapeutic methods in alien hand syndrome subtypes.

Subtype	Therapeutic methods	(Refs.)
Anterior alien hand syndrome	• Sensory tricks • Distracting tasks • Cognitive behavioural therapy	(21,48)
Posterior alien hand syndrome	• Visualization strategies • Spatial recognition tasks • Pharmacologic treatment: Clonazepam/botulinum toxin A	(49)
Callosal subtype of alien hand syndrome	Mirror box therapy	(49)
Alien hand syndrome associated with Parry-Romberg disease	Immunosuppressive therapy	(2)

Behavioural interventions and rehabilitation strategies work best when they are focused on the patient's needs. Both the patient and the caregiver need to be educated about the condition and then, based on the symptoms, the caregiver should try to provide the most beneficial treatment option. The patient has to be instructed to perform tasks that usually trigger the unwanted movements on the affected limb and then use coping strategies that may involve planning ahead the structure of the movement and also visualizing the movements of both hands and selecting the appropriate coping strategy. Several coping strategies can be used, including distracting the affected hand with an object or placing the affected hand in a box or restraining it while the other hand performs the required tasks (45).

Techniques like mirror box therapy, cognitive behavioral therapy and visuospatial coaching aim to restore control and alleviate distress. However, further research is essential to unravel the mysteries of this intriguing neurological phenomenon.

Prompt and aggressive immunosuppressive therapy, in order to prevent permanent brain damage and disability, can be used to treat AHS associated with Parry-Romberg disease, as the latter is presumed to have an autoimmune pathogenesis (46). This was shown by a case report of a 36-year-old Caucasian woman (45).

In a previous study, spatial recognition exercises led to an improvement in the symptoms of a patient with posterior AHS. The patient was first instructed to appreciate different shapes and spatial arrangements. He was later advised to transfer the acquired skills to his daily tasks, thus slowly improving his bimanual coordination (47).

Following a stroke, a 76-year-old man developed symptoms such as groping and grasping. These repetitive movements caused a lot of distress to the patient, particularly during the night, disrupting his sleep. In order to relieve the symptoms, an oven mitt was placed over the affected hand, leading to a significant improvement, which allowed him to sleep. The mechanism behind this trick was likely the sensory stimulation of the sensory spinal grasp reflex, causing an inhibition of the alien movements (48).

Mirror box therapy uses the principle of creating positive visual feedback by placing a mirror in between hands, which covers the affected limb and reflects the movement of the normal one. It is a rehabilitation modality that is based on tricking the brain by incorporating the mirror image as part of the body, and doesn't require any learning or preparation. The mirror box therapy is mostly used to improve motor behaviour when it comes to lesions of the corpus callosum (2).

In conclusion, the treatment options for AHS need to be adequately selected taking into account the localisation of the lesion that caused AHS, as well as the related psychiatric manifestations (such as depression or anxiety), since there is no known specific treatment. Caregivers should combine different strategies including muscle control therapies with botulinum toxin and neuromuscular blocking agents, benzodiazepines, behavioural and cognitive therapy techniques, mirror box therapy, learning task behavioural therapies and visuospatial coaching techniques.

Evolution and prognosis. The prognosis is better when AHS occurs secondary to a stroke or a brain illness, as compared with a neurodegenerative disease. The type of AHS with the best prognosis is the stroke-related one, where the patient-tailored rehabilitation can take up to 24 months (49).

The symptoms of AHS can last from several days up to several years. The shortest duration was observed in the case of a 77-year-old woman and was reported to be 30 min (49).

The manifestations of AHS may be delayed when the cause is an acute brain illness. By contrast, the alien hand symptoms associated with progressive degenerative cerebral disorders may last indefinitely or until the cerebral degeneration becomes so advanced that it interferes with hand mobility. It has been found that AHS may overlap with psychiatric symptoms, particularly in patients who have developed psychotic feelings of embarrassment and guilt in the context of a somatic pathology (49).

AHS is a rare neurological condition, whose manifestations can often overlap and be mistaken with those of psychiatric conditions. Further investigation into AHS is necessary in order to better understand the condition as well as to develop appropriate treatment plans. Taking into account the rarity of the affliction, ongoing studies on this matter may include relatively small numbers of participants; thus, further research is required in order to confirm the many facets of this condition. Clinicians should consider AHS as a pathological entity when facing a clinical picture that raises questions regarding neurological vs. psychiatric causes.

4. Conclusions

This study was conducted to present the current status of research on a rare condition that is AHS. Following a literature review, we aimed to summarise the importance of differential diagnosis with psychiatric conditions, as well as the main course of treatments and life quality improvement methods.

Future research into AHS should aim for a comprehensive analysis that includes an expanded range of sources, extending the database timeline to include studies prior to the year 2000, and broadening the patient age range to encompass those under 18 years of age.

AHS is a rare and diagnostically challenging neurological syndrome, often due to the complexity of corpus callosum injuries that coexist with other cerebral damage. The etiology of AHS is multifaceted, with patients frequently exhibiting a variety of comorbidities. Clinical presentations of AHS can vary significantly, with certain individuals experiencing transient symptoms and others more chronic. Ongoing interdisciplinary and meticulous evaluation is essential for managing this condition.

Currently, there is no specific treatment for AHS, although pharmacological and behavioural therapies have been shown to ameliorate symptoms and enhance the quality of life of patients. Prevention through the management of associated conditions, such as obesity, cardiovascular diseases and neoplasms, is also critical. It is vital to distinguish AHS from psychiatric disorders, as both can manifest as abnormal motor movements of the upper limbs. Despite the diverse causes of AHS, differential diagnosis of psychiatric conditions must always be a consideration, given the significant psychiatric implications associated with the disorder.

AHS is a rare neurological condition that presents unique challenges and learning opportunities for clinicians. Understanding AHS is crucial for accurate diagnosis and effective treatment. It offers insight into complex brain functions, such as motor control and self-awareness. The study of AHS can also contribute to our knowledge of other neurological disorders. Despite its rarity, AHS has significant implications for patient care, emphasizing the need for personalized treatment strategies. Therefore, continued research and clinical attention to AHS are essential in advancing neurological and psychiatric care.

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Competing interests

The authors declare that they have no competing interests.

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