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Tremor and Other Hyperkinetic Movements

Reviews

Pathophysiology and Treatment of Alien Hand Syndrome

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Abstract

Background: Alien hand syndrome (AHS) is a disorder of involuntary, yet purposeful, hand movements that may be accompanied by agnosia, aphasia, weakness, or sensory loss. We herein review the most reported cases, current understanding of the pathophysiology, and treatments.

Methods: We performed a PubMed search in July of 2014 using the phrases "alien hand syndrome," "alien hand syndrome pathophysiology," "alien hand syndrome treatment," and "anarchic hand syndrome." The search yielded 141 papers (reviews, case reports, case series, and clinical studies), of which we reviewed 109. Non-English reports without English abstracts were excluded.

Results: Accumulating evidence indicates that there are three AHS variants: frontal, callosal, and posterior. Patients may demonstrate symptoms of multiple types; there is a lack of correlation between phenomenology and neuroimaging findings. Most pathologic and functional imaging studies suggest network disruption causing loss of inhibition as the likely cause. Successful interventions include botulinum toxin injections, clonazepam, visuospatial coaching techniques, distracting the affected hand, and cognitive behavioral therapy.

Discussion: The available literature suggests that overlap between AHS subtypes is common. The evidence for effective treatments remains anecdotal, and, given the rarity of AHS, the possibility of performing randomized, placebo-controlled trials seems unlikely. As with many other interventions for movement disorders, identifying the specific functional impairments caused by AHS may provide the best guidance towards individualized supportive care.

Keywords: Alien hand, callosal variant, frontal variant, alien hand pathophysiology, posterior variant, alien hand treatment

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Introduction

Alien hand syndrome (AHS) is a higher-order, motor control disorder featuring involuntary, yet purposeful, movements.[1] The affected limb is typically the hand, although leg (alien limb phenomena) involvement has been reported.[2] In AHS there is a complex sense of limb foreignness,[3] including misidentifying the limb as the examiner's. Sometimes the limb is personified:[4] patients have named their alien hands.

By definition, the limb movements are not the result of movement disorders. They may be associated with other neurological deficits, including decreased motor spontaneity, speech hesitation, apraxia, tactile dysnomia, and behaviors associated with frontal lobe dysfunction.[5] The movements are sometimes so bizarre that they may be misinterpreted as functional.[4]

Common causes include anterior cerebral artery strokes,[6] midline tumors, and neurodegenerative illnesses. Rarer causes include spontaneous pneumocephalus,[7] migraine aura,[8] seizure,[9,10] and Parry–Romberg Syndrome, a presumed autoimmune disorder with progressive facial hemiatrophy.[11]

Theories on pathophysiology have evolved over the years. In this paper, we will review many of the published reports, discuss the current understanding of the pathophysiology, and reflect on the reported treatments.

Methods

We performed a PubMed search in July 2014 using the phrases "alien hand syndrome," "alien hand syndrome pathophysiology,"

"alien hand syndrome treatment," and "anarchic hand syndrome." The search yielded 141 papers, including reviews, case reports, case series, and small clinical studies. After excluding the 33 non-English reports without an English abstract, we included the remaining 109, regardless of publication date.

Results

Historical overview and classification

Advanced neuroimaging techniques allowed categorization of AHS into different variants. The study of these variants allowed the different mechanisms at play to be contrasted, and it was realized that clinical overlap is common. In this section we will recount the timeframe over which the different variants were recognized, describe their phenomenology, and discuss the theories and evidence behind their pathophysiology.

AHS was first described by Kurt Goldstein in 1908. He reported a patient who developed involuntary left hand movements after a stroke.[5] It was not until 1972, however, that Brion and Jedynak[12] first coined the term "alien hand" after observing three patients with callosal tumors who were unable to recognize their own hands. Multiple case reports and series have since been published. (Table 1)

Modern neuroimaging has demonstrated that lesions in different brain areas lead to AHS, resulting in phenomenological variations. In 1991, Dell Sala[13] described two forms: an "acute" form occurring after callosal lesions, and a "chronic" form caused by callosal and anteromedial frontal lesions.[13] Feinberg et al.[14] refined this idea and described two distinct syndromes: a frontal and a callosal variant.

Anterior variants

The two anterior variants are frontal and callosal subtypes. Patients with the frontal variant exhibit groping (where the hand seems to be constantly searching for nearby objects), grasping, or compulsive manipulation of tools.[15] The frontal variant results from lesions of the supplementary motor area (SMA), cingulate cortex, dominant medial prefrontal cortex, or the corpus callosum.

The callosal variant, in turn, arises mostly from callosal damage and often features intermanual conflict. Intermanual conflict (opposing purposeful movements of the patient's hands) is particularly common with lesions to the anterior third of the rostrum.[5,14] It is common to see the hands "fighting" against each other when trying to complete a goal-directed activity. Some examples include a strong grasp of the opposing hand, clumsy or mischievous actions interfering with tasks, or removing desired objects. These movements likely do not require high-level motor planning and probably ensue when inhibitory patterns are either not activated or not suppressed. It is also possible that these conflicting movements are elicited from the voluntary actions of the normal hand.

Callosal lesions also cause other disconnection syndromes. Geschwind and colleagues[16] reported a 68-year-old female who developed intermanual conflict days after a callosal infarction. Her symptoms evolved into an interhemispheric disconnection syndrome consisting of ideomotor apraxia, tactile anomia, and agraphic aphasia. This patient had delayed reaction times of the affected hand to visuomotor information.[16] Vascular lesions (hemorrhages from aneurysms or cerebral venous malformations),[15] demyelination (multiple sclerosis, Machiafava–Bignami syndrome), tumors (lipomas, gliomas, lymphoma), trauma (diffuse axonal injury), and surgery (callosotomy for refractory epilepsy)[17] can all cause disconnection syndromes.

Patients with callosal (but also rarely with frontal) AHS can exhibit autocriticism (frustration caused by intermanual conflict). Distress comes from the perception of onlookers, and patients frequently cover the alien limb by sitting on it.[5]

Posterior variant

A "posterior" variant, resulting from thalamic, posterolateral parietal, or occipital lobe damage, has recently been recognized.[18] These patients unintentionally withdraw the affected hand from environmental contact or stimuli (avoidance response) or experience uncoordinated hand movements or involuntary levitation,[18] which may be task specific. In a case of corticobasal syndrome (CBS), the patient had exaggerated arm elevation only while walking.[19] In another report, levitation was triggered by coughing or sudden noises.[20] Finally, a patient with left parietal infarction had arm levitation while supine, which worsened with pressure over the biceps tendon.[21]

The posterior variant can be accompanied by hemianesthesia, hemianopia, visuospatial neglect,[22] and optic ataxia.[23] Patients with parietal or thalamic lesions may have significant sensory deficits without weakness.[24] The affected hand can also have unusual postures with the digits hyperextended and the palmar surface pulling away from approaching objects.

The posterior variant is observed in different neurodegenerative conditions. Patients with AHS, agnosia, apraxia, and early-onset dementia likely have CBS secondary to Alzheimer's disease or a tauopathy, such as progressive supranuclear palsy.[25] In contrast, patients with acute or subacute, rapidly progressive AHS may have Creutzfeld–Jacob disease (CJD). A study recognized AHS in 4% of patients with CJD reported between 1976 and 2008, 85% of whom presented with AHS.[26]

As described, each variant has characteristic, distinguishing features (Table 2). However, patients may simultaneously demonstrate features of different variants. For example, a woman with a callosal hemorrhage extending to the medial frontal lobe was reported to have both intermanual conflict and compulsive grasping movements.[27] Coexisting intermanual conflict and sensory loss were reported in another patient with a callosal infarction.[22] Finally, mixed anterior and posterior AHS was described in two pathologically proven CJD cases, who had significant intermanual conflict and hemispatial neglect.[28]

From this historical overview it is evident that clinicopathological and imaging techniques aided our ability to subclassify AHS based on common causes. In the last 20 years our understanding of AHS subtypes has evolved to the three, well-defined variants we now accept: the two anterior (frontal and callosal) variants and one posterior.

Table 1. Summary of Reported Cases of Alien Hand Syndrome

Reference	Case No.	Diagnosis	Localization of Lesion or Imaging Findings	Hand	Diagnostic Dyspraxia or Intermanual Conflict	Grasping	Levitation	Groping	Utilization Behavior
Goldstein[69]		Infarction		L	X	X			
Akelaitis[70]	1	Callosotomy	Body of corpus callosum, genu of corpus callosum	L	X				
	2	Callosotomy	Complete section of corpus callosum	R	X				
Goldberg et al.[71]	1	Infarction	L medial frontal cortex	R	X	X		X	
	2	Infarction	L medial frontal cortex	R		X			X
Levine and Rinn[23]		Infarction	R temporal/occipital cortex, posterior thalamus	L				X	
McNabb, et al.[72]		Infarction	L superior and medial frontal cortex and parietal	R		X		X	
Banks et al.[36]	1	Gunshot wound	Medial frontal white matter bilaterally, corpus callosum, R basal ganglia, internal capsule and thalamus	L		X			
	2	Ruptured anterior communicating Artery Aneurysm	Genu of corpus callosum, bilateral medial frontal cortex, R gyrus rectus	L	X			X	X
Goldberg and Bloom[73]	1	Infarction	Body of corpus callosum, R medial frontal cortex, supplementary motor area, anterior cingulate gyrus	L	X	X			X
	2	Infarction	L medial frontal cortex, supplementary motor area, anterior cingulate gyrus	R		X		X	
	3	Infarction	Corpus callosum, R medial frontal cortex, supplementary motor area, anterior cingulate gyrus	L		X		X	

Table 1. Continued

Reference	Case No.	Diagnosis	Localization of Lesion or Imaging Findings	Hand	Diagnostic Dyspraxia or Intermanual Conflict	Grasping	Levitation	Groping	Utilization Behavior
	4	Infarction	Corpus callosum, L medial posterior frontal cortex, supplementary motor area, anterior cingulate gyrus	R		X		X	
Kuhn et al.[74]		Infarction	Body of corpus callosum, genu of corpus callosum, bilateral anterior medial frontal cortex, supplementary motor area	R		X			
Della Sala et al.[75]		Ruptured anterior communicating artery aneurysm	Anterior corpus callosum, bilateral frontal cortex, L medial frontal cortex, supplementary motor area	R		X		X	
Hanakita and Nishi[76]		Infarction	Corpus callosum, L medial frontal cortex, cingulate gyrus	L	X				
Feinberg et al.[14]		Infarction	Corpus callosum, L medial frontal cortex	R		X		X	
Gottlieb et al.[77]	1		Possible corpus callosum, R fronto-parietal cortex	L	X			X	X
	2		Body of corpus callosum, bilateral medial frontal cortex	L	X				
Leiguarda et al.[39]	1	Idiopathic cortical atrophy	L medial frontal cortex atrophy	R		X			
	2	Diffuse lymphocytic lymphoma	R medial frontal cortex	L		X			
	3	Seizures after the removal of an arteriovenous malformation	L posterior parietal cortex	R			X		

Table 1. Continued

Reference	Case No.	Diagnosis	Localization of Lesion or Imaging Findings	Hand	Diagnostic Dyspraxia or Intermanual Conflict	Grasping	Levitation	Groping	Utilization Behavior
	4	Ruptured arteriovenous malformation	R parietal/temporal cortex	L			X		
Dolado et al.[78]		Infarction	Bilateral parietal	L			X	X	
Green et al.[79]		Alzheimer's Disease	R parietal cortex, mild frontal	L					
Ventura et al.[80]		Hemorrhagic stroke	R capsulothalamic area, R frontal/temporal/parietal cortex	L			X		
Geschwind et al.[16]		Infarction	Body of corpus callosum, R cingulate cortex	L				X	
Giroud and Dumas[81]	7	Infarction	Corpus callosum, fronto-parietal ischemia	L		X			
	8	Infarction	R anterior corpus callosum, R frontal cortex	L		X			
Nagumo and Yamadori[82]		Infarction	L body of corpus callosum, genu of corpus callosum	L		X			
Papagno and Marsile[83]		Ruptured Anterior Communicating Artery Aneurysm	Anterior corpus callosum, R medial frontal cortex	L	X				
Chan et al.[2]		Infarction	Body of corpus callosum, genu of corpus callosum, isthmus of corpus callosum, R supplementary motor area, anterior cingulate gyrus, bilateral medial prefrontal cortex	L	X	X		X	

Table 1. Continued

Reference	Case No.	Diagnosis	Localization of Lesion or Imaging Findings	Hand	Diagnostic Dyspraxia or Intermanual Conflict	Grasping	Levitation	Groping	Utilization Behavior
Kischka et al.[84]		Infarction	Anterior corpus callosum, L medial frontal cortex, parieto-occipital, supplementary motor area	R		X		X	X
Tanaka et al.[85]	1	Infarction	Post body of corpus callosum, anterior splenium of corpus callosum, L cingulate gyrus, temporoparietal	L	X				
	2	Infarction	Body of corpus callosum, R cingulate gyrus, L anterior cingulate gyrus, bilateral medial frontal cortex	L	X			X	
	3	Infarction	Body of corpus callosum, genu of corpus callosum, L anterior cingulate gyrus	L	X				
	4	Infarction	Anterior body of corpus callosum, L medial frontal cortex, anterior cingulate gyrus	R		X		X	X
	5	Infarction	Anterior body of corpus callosum, L medial frontal cortex	R		X		X	
	7	Infarction	Anterior body of corpus callosum, R medial frontal cortex, anterior cingulate gyrus	L		X		X	X
Andre and Domingues[86]		Reversible ischemia	L internal capsule, R occipital cortex, L cerebellum	L				X	

Table 1. Continued

Reference	Case No.	Diagnosis	Localization of Lesion or Imaging Findings	Hand	Diagnostic Dyspraxia or Intermanual Conflict	Grasping	Levitation	Groping	Utilization Behavior
Chan and Ross[87]	1	Infarction	Genu of corpus callosum, isthmus of corpus callosum, L medial frontal cortex, supplementary motor area, anterior cingulate gyrus	R, L	X (L)	X (R)			
	2	Infarction	Body of corpus callosum, genu of corpus callosum, R medial frontal cortex, supplementary motor area, anterior cingulate gyrus	L		X		X	
	3	Infarction	Genu of corpus callosum–isthmus of corpus callosum, R prefrontal cortex, supplementary motor area, anterior cingulate gyrus	L	X	X		X	
Feinberg et al.[9]		Seizures in the setting of a glioblastoma multiforme	R frontotemporal cortex	L		X		X	
Nicholas et al.[88]		Infarction with hemorrhagic conversion	Corpus callosum	L		X		X	
Tow and Chua[89]		Infarction	L medial frontal cortex and posterior parietal cortex	R		X		X	
Ay et al.[90]		Infarction	Splenium of corpus callosum, R posterior frontal/temporal/occipital/parietal cortex, thalamus	L				X	
Groom et al.[52]		Infarction	R medial posterior temporal cortex, posterior parietal/occipital cortex	L				X	

Table 1. Continued

Reference	Case No.	Diagnosis	Localization of Lesion or Imaging Findings	Hand	Diagnostic Dyspraxia or Intermanual Conflict	Grasping	Levitation	Groping	Utilization Behavior
Marti-Fabregas et al.[91]		Infarction	R inferior parietal cortex	L		X		X	
Fisher[92]	1	Corticobasal syndrome		L, R	X (R)	X (L)			
	2	Corticobasal syndrome		R	X				
	3	Corticobasal syndrome		L	X		X		
	4	Corticobasal syndrome		L				X	
	5	Corticobasal syndrome		L, R	X (L)	X (both)			
	6	Corticobasal syndrome		L	X	X			
Ong Hai and Odderson[93]		Infarction	Anterior corpus callosum, R medial frontal cortex	L		X		X	
Bundick and Spinella[43]		Infarction	R posterior parietal/temporal cortex, medial frontal cortex	L			X		
Inzelberg et al.[94]		Creutzfeld–Jakob disease	Mild cerebral atrophy	L			X		
Carrilho et al.[3]	1	Corticobasal syndrome	R temporal/parietal cortex	L			X		
	2	Corticobasal syndrome	R temporal/parietal cortex	L			X		
	3	Alzheimer's disease	L parietal cortex	R			X		
	4	Infarction	R parietal cortex	L			X		

Table 1. Continued

Reference	Case No.	Diagnosis	Localization of Lesion or Imaging Findings	Hand	Diagnostic Dyspraxia or Intermanual Conflict	Grasping	Levitation	Groping	Utilization Behavior
Kumral[27]		Moya-Moya leading to a hemorrhage	Body of corpus callosum, genu of corpus callosum, splenium of corpus callosum, R medial frontal cortex (unclear)	L		X		X	
Nishikawa et al.[95]	1	Infarction	Body of corpus callosum, genu of corpus callosum, splenium of corpus callosum	L	X				
	3	Resection of a central neurocytoma via transcallosal and transcortical approaches	Anterior body of corpus callosum, splenium of corpus callosum, L parietal cortex	R				X	X
Lavados et al.[96]		Hemorrhage	Corpus callosum, F medial (inferred)	L, R	X (L or R)	X (R)		X (R)	X (R)
Suwanwela and Leelacheavasit[97]	1	Infarction	Body of corpus callosum, splenium of corpus callosum	L	X				
	2	Infarction	Body of corpus callosum	L	X				
Marey-Lopez et al.[50]		Infarction	R thalamus	L			X	X	
Pack et al.[68]		Infarction	R lateral thalamus	L			X		
Rohde et al.[20]		Presumed vascular-mediated cortical atrophy	L central/parietal cortical and subcortical lesions and extensive atrophy of the pre- and post-central gyri	R			X		
Pappalardo et al.[56]		Infarction	L cortical–subcortical parieto-occipital lobes	R	X	X			
Giovannetti et al.[37]		Infarction	L medial frontal extending into the corpus callosum	R	X	X		X	X

Table 1. Continued

Reference	Case No.	Diagnosis	Localization of Lesion or Imaging Findings	Hand	Diagnostic Dyspraxia or Intermanual Conflict	Grasping	Levitation	Groping	Utilization Behavior
Iwashita et al.[98]		Infarction	R frontal lobe	L					
Espinosa et al.[99]		Infarction	R parietal lobe and anterior corpus callosum	L	X				
Kikkert et al.[64]	1	Infarction	Presumed R parietal lesion	L	X		X		X
	2	Infarction	L frontal lobe in the area of the anterior cerebral artery	R	X	X			
Kurne et al.[100]		Multiple Sclerosis	Non-enhancing multiple hyperintense lesions in the corpus callosum, periventricular white matter and centrum semiovale on MRI	L			X		
Caixeta[101]		HIV	R frontal and parietal hypodensity on CT	L	X	X	X		
Bejot et al.[102]		Infarction	Bilateral hyperintense signals in diffusion-weighted images in the anterior cerebral artery territories involving the R anterior corpus callosum	L	X				
Kessler et al.[47]		Infarction	L anterior parietal lobule and posterior lip of post-central gyrus	R		X			
Soman et al.[103]		Infarction	R parietal lobe, dorsal putamen, and body of caudate	L	X				
Spector et al.[24]		Infarction	R parietal lobe	L				X	

Table 1. Continued

Reference	Case No.	Diagnosis	Localization of Lesion or Imaging Findings	Hand	Diagnostic Dyspraxia or Intermanual Conflict	Grasping	Levitation	Groping	Utilization Behavior
Haq et al.[61]		Brain herniation	R cerebral peduncle gliosis and L cystic anterior thalamus changes	R		X	X		
Takenouchi and Solomon[11]		Parry Romberg Syndrome	Progressive atrophy and gliosis of the R thalamus	L	X		X		
Kim et al.[104]		Infarction	R parietal	L	X			X	
Faber et al.[105]		Infarction	L paracallosal area	R	X				
Terazzi et al.[106]		Infarction	R thalamus and calcarine cortex	L	X	X	X		
Cantagallo et al.[65]		Hemorrhage	Fronto-basal area bilaterally, L fronto-opercolar area and L frontal superior area	R	X				
Prakash et al.[19]		Corticobasal syndrome	Asymmetrical R fronto-parietal cortical atrophy	L				X	
Pooyania et al.[62]		Infarction	L superior frontal gyrus	R	X	X			X
Bartolo et al.[51]		Infarction	L posterior thalamus, parahippocampal gyrus, inferior and posterior temporal lobe, lateral portion of the splenium of the corpus callosum, and cortical part of the occipital lobe.	R			X	X	
Yuan et al.[22]		Infarction	Genu, body and splenium of the corpus callosum	L	X				
Verleger et al.[42]		Infarction	L side of corpus callosum from genu to posterior isthmus	L	X				
Huang and Jia[15]		Cerebral venous malformation	Hemorrhage in the genu and body of the corpus callosum	L	X				

Table 1. Continued

Reference	Case No.	Diagnosis	Localization of Lesion or Imaging Findings	Hand	Diagnostic Dyspraxia or Intermanual Conflict	Grasping	Levitation	Groping	Utilization Behavior
Nandhagopa et al.[17]		Infarction	Bilateral parietal parasagittal areas initially, body of corpus callosum found to be involved later	L	X				
Rubin et al.[26]	1	Creutzfeld–Jakob disease	Diffuse cortical T2 signal on MRI	L					
	2	Creutzfeld–Jakob disease	Normal	L					
	3	Creutzfeld–Jakob disease	Bilateral striatum, diffuse cortex left hemisphere	R					
	4	Creutzfeld–Jakob disease	Normal	L					
	5	Creutzfeld–Jakob disease	Unknown	L					
	6	Creutzfeld–Jakob disease	R posterior parietal cortical hypoattenuation on CT	L					
	7	Creutzfeld–Jakob disease	Normal imaging	R					
	8	Creutzfeld–Jakob disease	Cortical and striatal DWI/ FLAIR hyperintensity Diffusely on MRI	L					
	9	Creutzfeld–Jakob disease	Bilateral L> R selective parietal restricted diffusion on MRI	R					
	10	Creutzfeld–Jakob disease	Restricted diffusion in bilateral striatal nuclei, left parietal cortex on MRI	R					
	11	Creutzfeld–Jakob disease	Diffuse restricted diffusion, T2 hyperintensity of R posterior hemispheric cortex on MRI	L					

Table 1. Continued

Reference	Case No.	Diagnosis	Localization of Lesion or Imaging Findings	Hand	Diagnostic Dyspraxia or Intermanual Conflict	Grasping	Levitation	Groping	Utilization Behavior
	12	Creutzfeld–Jakob disease	Restricted diffusion, T2 hyperintensity of bilateral R> L parietal, occipital lobes on MRI	L	X		X		
	13	Creutzfeld–Jakob disease	Diffuse cortical restricted diffusion on MRI	L					
Nash et al.[7]		Pneumocephalus	R frontal lobe	L					X
Hertz et al.[107]		Infarction	L posterior middle cerebral artery territory infarction	R	X				
Park et al.[1]	1	Infarction	L medial frontal white matter infarction	R		X			
	2	Infarction	R frontal lobe and anterior corpus callosum infarction	L	X				
Shereef and Cavanna[48]		Infarction	R posterior parietal	L					
Jang et al.[41]		Infarction	Anterior portion of the L cingulated gyrus and the corpus callosum (posterior portion of the genu to the anterior portion of the splenium)	R		X		X	X
Graff-Radford et al.[46]	108 cases	Corticobasal syndrome							
	14 cases	Cerebrovascular	Ischemic strokes, arteriovenous malformation and subdural hematoma						
	9 cases	Creutzfeld–Jakob disease							
	5 cases	Hereditary Diffuse Leukoencephalopathy with Spheroids							

Table 1. Continued

Reference	Case No.	Diagnosis	Localization of Lesion or Imaging Findings	Hand	Diagnostic Dyspraxia or Intermanual Conflict	Grasping	Levitation	Groping	Utilization Behavior
	4 cases	Tumor	Astrocytomas and oligodendroglioma						
	10 cases	Other							
McBride et al.[38]		Corticobasal syndrome	Asymmetric atrophy of L parietal regions	R		X			
Nowak et al.[67]	1	Infarction	L anterior corpus callosum, left anterior paramedian periventricular white matter and adjacent paramedian cortex	R	X	X		X	
	2	Infarction	L anterior corpus callosum and overlying white matter	R	X	X			
Lunardelli et al.[108]		Multiple Sclerosis	Multiple corpus callosal lesions, especially of caudal portion	L	X				
Chokar et al.[109]		Cerebral vasculitis	R hemispheric cortical and subcortical edema affecting the white matter and temporal, parietal, and occipital lobes	L		X			
Romano et al.[66]		Hemorrhage	L fronto-parietal hemorrhage	R			X	X	

Abbreviations: CT, Catscan; DWI, Diffusion-weighted Imaging; FLAIR, Fluid-attenuated Inversion Recovery; HIV, Human Imunodeficiency Virus; L, Left; MRI, Magnetic Resonance Imaging; R, Right; X, finding present in that case.

Table 2. Variants of Alien Hand Syndrome

Type	Commonly Affected Areas	Common Causes	Symptoms and Signs
Frontal	Supplemental motor area	Tumors	Groping
	Cingulate gyrus	Infarction	Grasping
	Corpus callosum	Trauma	Utilization behavior
Callosal	Corpus callosum	Callosotomy	Intermanual conflict
		Tumors	
		Infarction	
Posterior	Parieto-occipital cortices	Infarction	Levitation
	Thalamus	Creutzfeld–Jakob disease	Cortical sensory deficits
		Corticobasal syndrome	Abnormal posturing of the limb

Clustering these subtypes will likely allow us to continue to understand the mechanistic differences between these variants. The current evidence on the pathophysiology of the different AHS types will be discussed below.

Proposed pathophysiology and evidence from functional imaging

While no single observation explains every aspect of AHS, anecdotal evidence from stroke patients[29,30] and, more recently, functional imaging studies[31–33] suggest a pivotal role in the disruption of brain networks, as will be reviewed below.

AHS understood in terms of theories of motor control

Multiple structures are considered necessary for hand control and appropriate environmental interaction, including the SMA, anterior cingulate, medial frontal lobe, corpus callosum, and parietal lobe.[34]

Anecdotal evidence suggests a loss of bilateral hemispheric activation required for bilateral hand control.[35] An example of this is a woman with AHS, following a gunshot wound to the frontal lobes who had extensive bifrontal atrophy extending through the corpus callosum and subcortical structures at the time of AHS onset.[36]

Loss of inhibitory tone may also cause AHS. Giovannetti et al.[37] proposed that there are central systems that mediate routine actions, while others control higher-functioning tasks. This executive system is likely not solely lateralized to the frontal lobe or linked to the pre-motor system. Instead, it is likely a "supramodal" system involved in resolving conflicts between tasks and prioritizing actions based on the task at hand. These authors argue that a dysfunction in this system may cause AHS. The executive system, they suggest, is capacity limited, and may be overwhelmed when performing dual simultaneous tasks.[37] Thus, keeping a distraction-free environment and avoiding multitasking may optimize performance of the affected hand.[37]

Similarly, experimental investigations in a CBS patient with right AHS suggest that involuntary grasping behaviors might be due to exaggerated, automatic motor activation triggered by objects that afford actions. In this report, normal automatic inhibition of primed responses was found in the unaffected hand, but not in the alien limb. The authors concluded that grasping behaviors may result from exaggerated object affordance effects, due to disrupted inhibition of automatically evoked responses.[38]

Splitting of attention may worsen control of the alien hand. In an experiment,[34] a patient with AHS made mistakes while making a cup of coffee. The errors made by each hand were different. The right (alien hand) was easily distracted by nearby objects and was perseverative. The normal hand made substitution errors. The difference in mistakes made by either hand was explained by the motor systems of the right hemisphere being disconnected from the semantic knowledge of the left hemisphere. Interestingly, when an additional task was added, the right hand was even more perseverative and distracted by nearby objects, while the left hand's error pattern remained unchanged. This experiment suggested that in AHS there is a malfunction of the inhibitory mechanisms of the medial pre-motor area, preventing the hand from reaching for nearby distracting objects.

Structures involved in anterior AHS

The SMA, involved in frontal AHS, receives inputs from cortical and subcortical regions and is involved in actions requiring selection between different tasks and sequencing events.[34] It is involved in motor planning and control of internally generated motor sequences. It has widespread connections to the primary motor cortex, pre-motor cortex, and subcortical motor areas. It also has reciprocal motor connections to the contralateral SMA. The SMA may suppress bilateral limb motor activity by inhibiting both motor cortices, and its electrical stimulation resulted in simple, repetitive, or complex movements. SMA stimulation may also cause patients to feel puzzled about being unable to perform their intended behavior.[39] Lesions to the SMA possibly result in the release of the ipsilateral motor cortex from this inhibitory control.

The cingulate gyrus is presumably implicated in compulsive, goal-directed motor behaviors;[40] epileptic discharges of gigantopyramidal neurons caused paroxysmal, forced grasping motions of the contralateral arm.[40] This gyrus may also influence the force and extent of these grasping responses[5] and contributes to the sense of foreignness in the anterior variants.[41]

Disruption of interhemispheric inhibition secondary to callosal damage, however, may also cause an alien sensation, usually of the non-dominant hand.[16] Coordinated movements of this hand require transfer of information from the bilateral frontal areas through the anterior corpus callosum.[16]

Incomplete bihemispheric suppression of motor control possibly leads to involuntary hand movements.[10] Electrophysiology studies support this disinhibition. Electroencephalography (EEG) studies in a callosal AHS patient revealed a reduced N1 component of the EEG potentials on the right side, implying faster visual processing of the right hemisphere before impulse control mechanisms could exert their effects.[42] Callosal disease may cause an inability of the intended hand to execute an action, while the opposite hand automatically produces the action.[35]

Structures involved in posterior AHS

Posterior AHS likely results from multiple cortical and subcortical lesions, leading to involuntary movements in the setting of sensory ataxia and poor proprioceptive awareness.[43] Hemineglect and disturbances in body schema may further contribute to a feeling of limb foreignness.

Gabarini et al.[44] noted body schema distortions when patients with left hemiparesis incorporated an examiner's arm, which had been placed in an egocentric (body-centered) position, into their own sensory–motor pathways, resulting in interference with normal right hand tasks. To better define this embodiment, they performed a controlled study with eight patients with left hemiparesis and AHS,[44] three of whom had abnormal embodiment. The hemiparetic patients were asked to draw lines with their right hand and circles with their affected left hand simultaneously. They were compared with 10 healthy control volunteers, who drew lines and circles with both hands, which resulted in bimanual coupling from the normal functioning of intentional programming of both healthy hands. The patients without abnormal embodiment showed no bimanual coupling, as they could not activate their injured motor programs during the bimanual task. However those with AHS and altered embodiment had a coupling effect for egocentric movements, suggesting that embodying the examiner's hand as their own altered the sensory–motor programming for their real limb.

Cortical parietal pathology can cause posterior AHS. The parietal lobe informs us about an object's size, shape, distance, and direction. It is also necessary for goal-directed behavior and formation of appropriate proprioceptive schemes. Impairments lead to proprioceptive errors, inability to perform goal-directed tasks, and excess sensitivity to unimportant tasks.[34]

The superior and inferior parietal lobules are both activated during coordinated hand movements. The inferior parietal lobule is a multimodal association area that receives inputs from multiple centers, including the primary somatosensory and prefrontal cortices, and subsequently relays output through multiple centers, including the basal ganglia and pontine nuclei. The superior parietal lobule, in turn, seems to assist in the integration of body image. Disruption of the intricate network between these lobules may cause AHS by interfering with normal responses to extrapersonal space.[45]

Patients with CBS frequently have parietal pathology, and will commonly manifest limb apraxia, cortical sensory deficits, or AHS. In a large Mayo Clinic study of patients with AHS from 1996 to 2011, 150 patients met the definition for AHS.[46] Of these, 108 had CBS, and the remaining 42 had cerebrovascular disease, progressive multifocal leukoencephalopathy, unspecified demyelinating disease, and posterior reversible encephalopathy syndrome. These cases consistently showed parietal and adjacent white matter lesions that were contralateral to the affected hand. This report suggested that disconnection of the parietal lobe from motor centers likely led to misperception by these other hemispheres, resulting in a feeling of loss of awareness of movement.[46]

Through the description of a patient with an acute left parietal stroke, Kessler and colleagues[47] proposed a precise localization of AHS. On the basis of their observations, they suggested that the posterior lip of the post-central gyrus, which is involved in kinesthesia, and Brodman area 5, which corresponds to the tertiary somatosensory cortex and is involved in stereognosis, may cause both the abnormal sensations and movements of an alien limb.[47]

It is interesting that involvement of the cortico-striato-thalamic circuitry, without significant parietal lobe injury, may also cause posterior AHS. This arises presumably from a combination of sensory ataxia and poor proprioceptive awareness.[48,49] This theory is supported by a case of extensive posterior cerebral artery (PCA) infarction that damaged the right occipital lobe, thalamus, and splenium of the corpus callosum. Along with AHS the patient had hemineglect and cortical sensory loss. She displayed signs of "triple ataxia," due to a combination of sensory ataxia (from damage of the ventral posterolateral thalamus), cerebellar ataxia (from damage to the dentatorubrothalamic tract), and optic ataxia (due to damage to the splenium and occipital cortex). She exhibited uncoordinated self-stimulatory arm movements, such as hitting her face or attempting to strangle herself. The movements likely resulted from misguided motor plans in response to emotions, which were affected by poor postural adjustments from the triple ataxia. Of note, fludeoxyglucose (FDG) positron emission tomography (PET) demonstrated hypometabolism of the infarcted regions and the right posterior fronto-parieto-temporal region.

A single thalamic lesion may result in AHS, as demonstrated by a case of posterior AHS from a right thalamic infarction, affecting the ventral posterior, ventral lateral, and dorsomedial nuclei. The thalamus has wide-ranging, reciprocal connections, and lesions may give rise to sensory and cerebellar ataxia, visuospatial dysfunction, and

hemineglect, all contributing to the development of AHS.[50] In another report, a patient with a left posterior thalamic lesion extending to the posterior corpus callosum, posterior temporal lobe, and parts of the occipital lobe also produced AHS with minimal sensory loss but without cerebellar ataxia or neglect. The authors attributed the AHS to the thalamic lesion's disruption of the experience of body schema, by its disconnection from the somatosensory cortex, and also by its disconnection from the remaining circuitry involved in producing voluntary actions. This circuit includes the frontal lobes, basal ganglia, and cerebellum.[51]

PCA infarctions may in fact create distinct perceptions of the alien limb. In a case of a right PCA stroke, the patient had ego-syntonic (acceptable or consistent with one's personality), rather than ego-dystonic (repugnant or inconsistent with one's personality) feelings toward his alien hand.[52] The authors argue that damage to the medial paralimbic fibers may produce a sensation of foreignness, similar to a corpus callosal lesion. Of note, medial paralimbic fibers originate from the hippocampus and basal ganglia and extend to the anterior cingulate, which was implicated in limb awareness.

Our understanding from structural and functional imaging

Reports of patients with AHS undergoing diffusion tensor tractography (DTT), an advanced structural imaging technique providing three-dimensional fiber tract visualization, shed light into the extensive connectivity of the corpus callosum. Jang et al.[41] reported a 72-year-old female who developed impulsive grasping, manipulation of objects, and involuntary reaching for objects 4 weeks after a left anterior cingulate and corpus callosal infarction. DTT revealed significant disruption of callosal fibers, except for those in the anterior genu and posterior splenium, which still had bilateral frontal and occipital connections, respectively.[41] In another case, a woman with a callosal hemorrhage demonstrated significant disruption of the interhemispheric fibers from the anterior part of the genu and much of the midbody of the callosum. However, the splenium and posterior part of the genu retained their connections to the bilateral occipito-temporal and frontal lobes, respectively. Those fibers connecting to both temporal lobes did so through the inferior fronto-occipital fasciculus, suggesting a possible redistribution of connectivity following callosal damage.[53]

FDG-PET suggested a more widespread involvement in controlling and inhibiting an alien limb. Involuntary action of an alien limb in a CBS patient caused activation of the primary motor cortex, pre-motor cortex, cerebellum, precuneus, and right inferior frontal gyrus (IFG). During voluntary action of the alien hand, both the right and the left precuneus were activated, but not the IFG. Also, when the patient performed conscious activities greater effort and concentration to perform tasks with the alien hand was required. Neither the precuneus nor the right IFG was activated by the healthy hand as neither is activated in normal motor paradigms. In fact, the precuneus is associated with first-person perspective taking, self-processing operations, and experience of agency. Thus, the precuneus represents an area of conflict of agency, as it was activated in both involuntary and voluntary tasks of the affected hand, suggesting a role in both inhibition and control of the alien hand. The right IFG is likely an inhibitory control center of volitional actions, and its activation in unwanted movements likely also represents another conflict of agency.[54]

In a FMRI (functional MRI) stud of a patient with left AHS following a right parietal lesion, voluntary and involuntary movements of the alien hand were compared. The voluntary movements of the alien hand correlated with activation of a wide network, including the contralateral primary motor cortex, left IFG, bilateral prefrontal cortices, and bilateral parietal cortices. The involuntary movements, however, only strongly activated the primary motor cortex. These findings suggest that although the primary motor cortex is activated in both types of movements, its activation alone is not responsible for subjective ownership of the movements because of its disconnection with the parietal cortices, leading to a lack of goal-directed movements.[55]

Similarly, a study measuring regional cerebral blood flow (rCBF) using single-photon emitted computed tomography (SPECT) in seven patients with CBS, six with left-hand symptoms, demonstrated reduced rCBF in the right parietal region compared with controls. Interestingly, three of the seven patients with CBS had AHS, and these also had reductions in the right thalamus, supramarginal gyrus, and the posterior cingulate gyrus.[32]

Mixed variants adding to the complexity of AHS

Motor phenomenology does not always correlate with the expected localization of the causative lesion. One example is a case of a patient with a posterior parieto-occipital region infarction causing intermanual conflict. This patient's AHS was likely due to the damage of the outflow of information from the parietal to the frontal cortices.[56] Trojano et al.[57] described a patient with a right mesofrontal stroke who presented initially with left-handed intermanual conflict and groping behaviors, but who eventually demonstrated resolution of the "alien feeling" and intermanual conflict, while the frontal behaviors persisted. This change in phenomenology suggests that there may be a functional rearrangement of interhemispheric motor pathways and of eventual interhemispheric callosal transfer.

A different patient with callosal infarctions exhibited groping and grasping maneuvers of the right hand, while intermanual conflict was present in the left hand. While the anterior callosal lesion (along with presumed temporary ischemia of the left frontal lobe) likely explained the right-handed symptoms, the left-hand involvement again suggested that the non-dominant hemisphere is under bilateral control.[16,58]

Perhaps even more extreme than these cases are the few reports where the localization of the lesions cannot be predicted at all by the phenomenology, such as AHS developing after a left pontine hemorrhage.[59] The authors argued that deafferentiation of proprioceptive pathways in the brainstem was the likely cause. Likewise, a recent functional imaging study in a CBS patient identified the medial frontal–prefrontal network to be implicated in altered awareness and motor control, as opposed to posterior circuits, as may be expected in this condition.[60]

Table 3. Treatment Modalities Described in Different Alien Hand Syndrome Variants

Variant	Therapeutic Modality
Anterior	Sensory tricks
	Distracting tasks
	CBT for anxiety control
	Verbal cues
Posterior	Botulinum toxin A
	Clonazepam
	Visualization strategies
	Spatial recognition tasks

Abbreviation: CBT, Cognitive Behavioral Therapy.

Summary of clinico-anatomic correlations

Although there are methodological differences between the different papers cited, the evidence seems to suggest that most cases of AHS arise from the disruption of interhemispheric connections, and/or of the connections between the frontal areas and the parietal lobes. The localization of the causative lesion may correlate with the phenomenology exhibited by the patient, although exceptions are common. Reports of overlap argue in favor of shared mechanisms between AHS subtypes, but the description of cases in patients with lesions distant from the usual involved areas reflects our incomplete understanding of the mechanisms causing AHS.

Reported treatments

There are no approved or recommended therapies for AHS, and its management is based on anecdotal reports of both pharmacologic and behavioral interventions (Table 3). A notable report is that of a 13-year-old female with right-arm levitation, after a left anterior thalamic infarction, who responded to clonazepam and botulinum toxin. Two days after starting 1 mg of clonazepam daily, she had a 70% reduction in the number of levitations per minute (LE/min) and spontaneous grasps per minute (SG/min). Unfortunately, poor tolerance prompted discontinuation. She subsequently received 600 units of botulinum toxin type A into the deltoid, triceps, biceps, flexor carpi ulnaris, and finger extensors of the right arm, which caused an 80% improvement in the LE/min and SG/min. Clonazepam possibly potentiated her thalamic GABAergic circuitry, which likely resulted in either reducing the arm's oversensitivity to external stimuli or dampened the internal stimulus driving the AHS. In contrast, botulinum toxin possibly helped either by weakening the arm or by altering sensory feedback.[61]

In terms of rehabilitation strategies, treatments focusing on the patient's needs are most beneficial. In one report of a man with a left superior frontal stroke and right AHS, educating the patient and caregiver about his condition, providing coping strategies (such as distracting the affected hand with an object), and using visualization tactics allowed him to regain his functional independence. These tactics focused on planning, visualizing every movement of both hands during the task, and organizing the sequences of the task. In addition, he was instructed to perform tasks that would trigger unwanted actions by the affected hand and subsequently cued to perform coping strategies, such as placing the hand in his pocket or distracting it with a ball. The outcomes from these interventions were measured with the functional index measure, which improved from 83 out of 126 to 119 out of 126.[62] Similar success from avoidance coping mechanisms was reported in a patient with AHS following resection of a frontal tumor. In this report, the patient was prompted to hold on to large stationary objects to occupy the alien hand while his normal hand performed daily tasks.[63]

In two patients with vascular lesions, behavioral modifications improved quality of life. In a patient with a right hemispheric stroke, placing the left hand in the right hemispace or restraining it while performing tasks was beneficial. Meanwhile, a patient with a left frontal lesion was able to control her anger and frustration about the involuntary movements with cognitive behavioral therapy. This allowed her to better utilize the affected hand.[64]

Another patient with posterior AHS improved with spatial recognition exercises; the patient was trained first to recognize different shapes and spatial arrangements and later to transfer the acquired skills to his daily tasks, thus potentially improving his bimanual coordination.[56]

Anecdotally, verbal cues ameliorated symptoms of AHS.[65] In this report, a patient was asked to accurately and quickly perform both exogen ous (in response to a stimuli) and endogenous (internally predetermined, sequential responses) tasks. The patient performed poorly in endogenous tasks with the affected hand. The errors only increased with the number of distractions. However, when verbal cues were added to the endogenous tasks, the patient performed better.[65]

Visual reinforcement may aid in controlling abnormal movements. In a patient with right AHS, placing the affected hand in a mirror box so that it may not only "see" the normal hand but also be confined in space allowed better control of both gross and fine movements, such as finger tapping. However, long-term benefits of this therapy are not known and it is possible that only posterior AHS may benefit due to reliance on sensorimotor integration.[66]

A sensory trick may also alleviate symptoms. A 67-year-old male with AHS following a stroke developed groping and grasping movements of his left hand that disrupted his sleep. To alleviate his distress, a simple oven mitt was placed over the hand, and his movements significantly improved, allowing him to sleep comfortably. The oven mitt likely provided enough stimulation for the sensory spinal grasp reflex to achieve accommodation, thus inhibiting the movements.[10]

Despite all of these anecdotal reports, long-term data on rehabilitation are scarce. In two patients with frontal AHS, gradual improvement of grasping and groping at 6 months was reported. Unfortunately, the strategies used in therapy, including using both

hands for tasks and suppressing involuntary movements, were not retained by the patients long-term. Despite that, the caregivers did report gradual improvement in AHS symptoms at their follow-up visits.[67]

Similarly, our limited understanding of the pathophysiology of AHS makes it difficult to accurately predict its natural history. Data from mixed variants suggest that callosal forms likely resolve faster than frontal variants.[57] Another case suggested good prognosis in those with posterior AHS from strokes without significant intervention.[68]

Discussion

Despite having been recognized as a clinical entity over a century ago, AHS continues to be a challenge. Our understanding of underlying mechanisms remains incomplete, but evidence from pathological and functional neuroimaging studies suggests a role for network disruption causing bihemispheric disinhibition and/or inter-hemispheric disconnection. Depending on the variant and the underlying pathology, apraxia, neglect, cortical sensory deficits, and other neurologic abnormalities may also be present in varying degrees, likely explaining the considerable phenotypic variability among patients. Functional imaging studies likely will continue to expand our knowledge of the pathophysiology of AHS, but the limited number of patients in these studies and the diverse underlying pathologies should raise caution when attempting to generalize their results. Repeated comprehensive neuropsychological testing and long-term follow-up may further expand our knowledge about the evolution of AHS in the future.

In general, there are broadly distinctive features for each of the variants (Table 2). However, our review reveals that patients can exhibit mixed phenotypes, and, at times, their symptoms may not be localizable. Thus, trying to classify patients into one of these broad categories clinically, although academically interesting, may not be indispensable when managing these patients.

There is limited evidence of medications benefiting AHS. Benzodiazepines and botulinum toxin injections were reported useful, but the majority of interventions described were behavioral. These include patient and caregiver education, visuospatial coaching techniques, distraction of the affected hand, and cognitive behavioral therapy. These recommendations are largely anecdotal, usually lack long-term follow-up, and represent evidence level C or D (Table 3). Unfortunately, given the rarity of AHS, the possibility of performing randomized, placebo-controlled trials with large numbers of patients sharing underlying pathologies seems unlikely.

Although Table 3 describes treatments for the different variants, we propose that the management of these patients should focus on identifying the specific functional impairments caused by AHS (regardless of the variant), and using a multidisciplinary approach to address them. We believe anxiety and fear should be addressed not only with anxiolytics but with appropriate behavioral therapies, guided by knowledgeable psychiatrists and psychologists. When and if the movements interfere with their activities, botulinum toxin, limb distraction or restraint, or retraining the hand (if possible) all seem reasonable interventions to consider. Finally, as with other movement disorders, physical and occupational therapies are crucial in teaching the patient and their caretakers to adapt to their new limitations.

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