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ORIGINAL COMMUNICATION

The alien limb phenomenon

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Abstract Alien limb phenomenon refers to involuntary motor activity of a limb in conjunction with the feeling of estrangement from that limb. Alien limb serves as a diagnostic feature of corticobasal syndrome. Our objective was to determine the differential diagnoses of alien limb and to determine the features in a large group of patients with the alien limb with different underlying etiologies. We searched the Mayo Clinic Medical Records Linkage system to identify patients with the diagnosis of alien limb seen between January 1, 1996, and July 11, 2011. One hundred and fifty patients with alien limb were identified. Twenty-two were followed in the Alzheimer's Disease Research Center. Etiologies of alien limb included corticobasal syndrome ($n = 108$), stroke ($n = 14$), Creutzfeldt Jakob disease ($n = 9$), hereditary diffuse leukoencephalopathy with spheroids ($n = 5$), tumor ($n = 4$), progressive multifocal leukoencephalopathy($n = 2$), demyelinating disease ($n = 2$), progressive dementia not otherwise specified ($n = 2$), posterior reversible encephalopathy syndrome ($n = 1$), corpus callosotomy ($n = 1$), intracerebral hemorrhage ($n = 1$) and thalamic dementia ($n = 1$). Ten of 14 cerebrovascular cases were right hemisphere in origin. All cases involved the parietal lobe. Of the 44 patients with corticobasal syndrome from the Alzheimer's Disease Research Center cohort, 22 had alien limb, and 73 % had the alien limb affecting the left extremities. Left sided corticobasal syndrome was significantly associated with the presence of alien limb ($p = 0.004$). These findings support the notion that the alien limb phenomenon is partially related to damage underlying the parietal cortex, especially right parietal, disconnecting it from other cortical areas.

Keywords Alien limb · Corticobasal syndrome

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Introduction

The alien limb, as defined by Doody and Jankovic [14], is characterized by an extremity that "is foreign" or "has a will of its own," together with observable involuntary motor activity. This phenomenon has intrigued physicians since its original description over 100 years ago [20]. The sense of estrangement was not emphasized or even recognized until 1972, when Brion and Jedynak [9] described the *main étrangère*, or "strange hand." They categorized this as a sensory disconnection syndrome and specifically a sign of callosal disconnection, noting the patients' inability to recognize their own hand when both hands were placed out of view (behind the back, or in front of the patient with closed eyes). Later Wilson et al. [42] offered an alternative name to the sign, "the stranger's hand sign," emphasizing the feeling of estrangement from one's limb. The term alien hand was introduced by Bogen as the result of a misinterpretation of Brion and Jedynak's paper [7, 43]. He expanded the definition to include undesired movements, redefining it as an action. In the decades between these descriptions and to the present, there has been an effort to better characterize this phenomenon in numerous disparate clinical scenarios, including stroke [1, 3, 10–12, 14, 15, 17–19, 22, 27, 29, 30, 34, 40, 41], corticobasal

syndrome (CBS) [14, 16, 26], progressive supranuclear palsy [5], Alzheimer's disease [4] and Creutzfeldt-Jakob disease (CJD) [23, 32, 33, 37]. Whereas alien limb phenomenon is typically described in one of the upper extremities, alien limb can also manifest in the lower extremity [24].

Earlier reports focused on alien limb as the result of callosal lesions. The anatomical studies [11, 15, 18, 29] involved mostly patients with anterior cerebral artery strokes, ischemic or hemorrhagic, that affected the genu of the corpus callosum with or without destruction of medial frontal structures. One unique case of non-fluent progressive aphasia progressing to corticobasal syndrome demonstrated spreading of atrophy to the medial frontal lobe and bilateral basal ganglia coinciding with the appearance of alien limb [21]. As more manuscripts were published, it became apparent that the presentation of alien limb came in several clinical phenotypes and an attempt was made to separate these patients based on lesion localization and clinical phenotypes [15]. The frontal alien hand syndrome was characterized by reflexive grasping and compulsive manipulation of tools and only occurred in the dominant hand [31, 38]. This particular syndrome was said to require injury to the dominant medial frontal structures as well as the anterior corpus callosum and was best explained by prominent exploratory reflexes by the dominant hand and release of non-dominant frontally-generated inhibition of that limb. The other variant was referred to as the callosal alien hand syndrome, which predominantly featured an intermanual conflict, termed diagonistic dyspraxia or callosal apraxia [17, 22, 41]. Rigid classifications have since come into question [40].

Recent reports detail the posterior alien limb phenotype, featuring coexisting rigidity, apraxia, cortical sensory findings, neglect and prominent estrangement from the limb. This variation has been termed the posterior alien limb and has been described in several diseases, most commonly in corticobasal syndrome (CBS) [14, 16, 26], but also in stroke [27], and Creutzfeldt-Jakob disease [32, 37]. The alien limb in CBS was more associated with limb elevation and abnormal posturing than that seen in disease processes affecting predominantly the frontal lobes or corpus callosum. Denny-Brown et al. [13] described the phenomenon of levitation in parietal lobe lesions, although Riley et al. [36] noted in one of the first clinical descriptions of CBS that the alien limb in CBS was similar to that described in lesions of the supplementary motor area. Alien limb was included as part of the proposed clinical phenotype of probable CBS in recent criteria for corticobasal degeneration [2].

The myriad of reports of alien limb cited above demonstrate that individual cases often defy exact classification, with considerable overlap of clinical, radiographic and pathologic findings. These findings, in the setting of decades of focused research attention failing to pinpoint a lesional "center," suggest that the quest for an individual clinical definition or neuroanatomic correlate to the alien limb is Sisyphean. However, the alien limb is used as an important feature in the diagnosis of CBS.

No prior studies have systemically assessed the occurrence of alien limb across a number of different etiologies and, thus, neuroanatomic locations. The aim of our study, therefore, was to determine the clinical and demographic features of a large number of subjects with the alien limb spanning all possible etiologies with an emphasis on the clinical features of those with CBS and alien limb.

Methods

Participants

Using the Mayo Clinic Medical Records Linkage System, we identified all patients with diagnoses of alien limb seen within the Department of Neurology between January 1, 1996, and July 11, 2011. The computer search strategy employed the text words "alien hand", "anarchic hand," "alien," and "mind of its own" crossed referenced with Department of Neurology. We identified 452 patients using this search strategy. The medical records of these 452 patients were reviewed to determine whether the patients met the Doody–Jankovic [14] diagnostic criteria: the patient experiences that an extremity "is foreign" or "has a will of its own," together with observable involuntary motor activity. Exclusion criteria included age less than 18 or features associated with alien limb such as mirror movements or arm levitation without meeting full Jankovic criteria. Of these 452 patients, 180 were thought to have features of alien limb syndrome. However, thirty patients were excluded because the documentation was insufficient to be certain whether they fulfilled clinical criteria, leaving a total of 150 patients with alien limb. Twenty-two of the 150 cases had been followed longitudinally in the Mayo Clinic Alzheimer's Disease Research Center (ADRC). All patients consented to the use of their clinical records for the purpose of research and the study was approved by the Mayo Clinic Institutional Review Board, and have, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

All cases of CBS (with and without alien limb) in the ADRC were included and used to determine the frequency of alien limb in CBS. A total of 44 patients with CBS had been evaluated by Mayo ADRC staff at least once.

Clinical data abstracted for all patients included age at onset of alien limb, description of alien limb, associated exam findings, gender, handedness, side of alien limb, first

and final clinical diagnosis, physical/neurological findings on examination, imaging studies and any treatment received. The CBS was defined as the classic clinical syndrome originally described by Rebeiz et al. [35], characterized by progressive asymmetric limb rigidity and apraxia, but allowing for overlap with other related syndromes; such as vertical gaze palsy/falls seen in progressive supranuclear palsy or aphasia seen in primary non-fluent aphasia. A Chi square analysis was performed to determine whether CBS laterality was associated with alien limb.

Imaging

All cases with stroke as the etiology for alien limb that had adequate quality structural MRI available were used for the lesion mapping analysis. The sequences acquired around the time of symptom-onset, with clinically-attributable infarction signal change were utilized. The unified segmentation and normalization procedure of SPM5 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, UK) was used to normalize every scan of interest to the ICBM template. Regions of interest (ROI) were then manually outlined for each subject's zone of infarction using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/). For simultaneous viewing of all nine cases, the ROIs were overlaid on the template brain (Fig. 1a). A map of the regional involvement across all of the subject's zones of infarction was created by combining all of these ROIs into a single frequency map (Fig. 1b) and displayed on a surface rendering using Caret software (http://www.nitrc.org/projects/caret/).

Neuropathology

The pathologic findings were characterized for each case that underwent brain biopsy or autopsy.

Results

Subjects

The demographic features are summarized in Table 1. The most common cause of alien limb was CBS ($n = 108$). In several cases of CBS, there was clinical overlap between CBS and other clinical presentations. Thirteen cases overlapped with PSP, seven with posterior cortical atrophy, two with primary progressive aphasia, and four had features of a presumed synucleinopathy (multiple system atrophy or dementia with Lewy bodies) in addition to CBS.

Ten patients with alien limb had a less common primary diagnosis including progressive multifocal leukoencephalopathy ($n = 2$), demyelinating disease not otherwise specified ($n = 2$), progressive dementia not otherwise specified ($n = 2$), posterior reversible encephalopathy syndrome ($n = 1$), corpus callosotomy for intractable seizures ($n = 1$), thalamic dementia ($n = 1$) and intracerebral hemorrhage complicated by hydrocephalus ($n = 1$). Figure 2 depicts cases with radiographic changes associated with the alien limb among different pathologies.

Table 2 summarizes the clinical features associated with alien limb amongst different diagnoses.

Table 3 provides examples of the clinical description of alien limb.

One hundred and twenty-two subjects had isolated upper extremity alien limb. Thirteen subjects had isolated leg alien limb. Twelve subjects had arm and leg involvement ipsilaterally. Three subjects had bilateral alien limb.

Time from disease onset to alien limb

Approximate time from first clinical symptom to appearance of alien limb was available for 110 subjects. Forty-six subjects had alien limb within 1 month of onset of disease. The CBS patients presented at a median of 12 months from disease onset; hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) subjects presented at a median of 9 months while CJD and stroke subjects presented with alien limb at disease onset. See Table 1 for further details.

Location of tumor and strokes with alien limb

There were 14 cerebrovascular cases and four tumors with alien limb. Table 4 describes the location of the stroke or tumor which resulted in alien limb. Ten cerebrovascular cases were right hemisphere while four were left hemisphere in origin. All cases involved the parietal lobe with occasional frontal, temporal, occipital lobe involvement. Figure 1 highlights the neuroanatomical regions most commonly involved in alien limb caused by stroke. Three of four tumors were right hemisphere while one was bilateral hemispheres. All tumors involved the parietal lobe with 2 of 4 also extending into the frontal lobe.

ADRC corticobasal syndrome cohort

All 44 CBS cases from the ADRC were assessed. Of these, 23 had left limb predominant CBS (21 right limb predominant CBS).

Alien limb in ADRC corticobasal syndrome cohort

Half (22) of the 44 CBS patients from the ADRC had alien limb. There was no significant difference between mean ages of disease onset (age 61.5 (8.28) with alien limb,

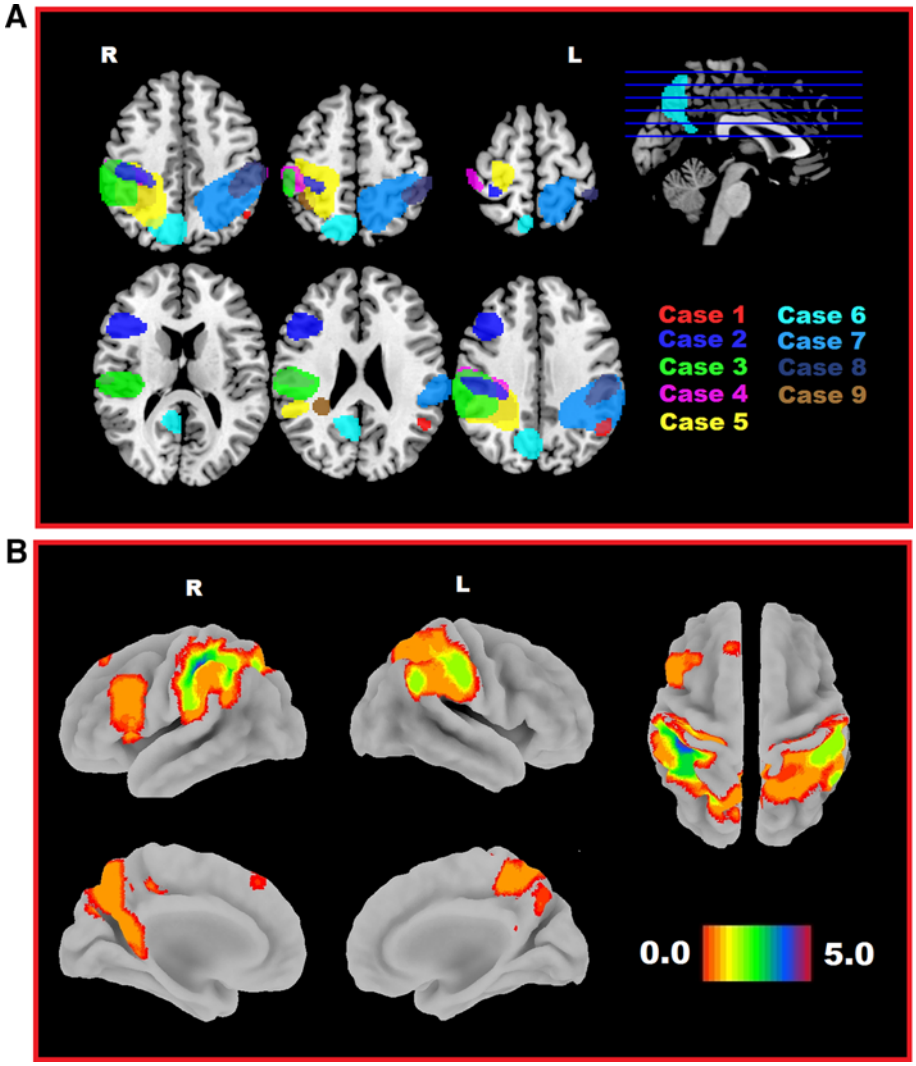

Fig. 1 Regional infarct distribution. The location of the zones of infarction are displayed on a template brain and color coded by case (**a**). The regional frequency of involvement across the brain in each of these nine cases is displayed by projecting the frequency of lesion overlap onto a surface rendering (**b**). Regions of the brain with only a single case involved are on the *orange* end of the spectrum and the region of the right parietal lobe with the maximum number of cases overlapping (5 of the 9) is on the *blue/violet* end of the spectrum. These cases correspond with cases 1–9 from Table 4

Table 1 Patient characteristics

	Etiology						
	CBS	Cerebrovascular	CJD	HDLS	Tumor	Other	Total
Number of patients	108	14	9	5	4	10	150
Female (%)	53	36	33	80	50	50	51
Handedness: right, left, ambidextrous (%)	96, 4, 1	93, 0, 7	89, 11, 0	80, 20, 0	75, 25, 0	100, 0, 0	95, 4.5, < 1
Median Age at Alien Limb Onset (range)	65 (41–84)	65 (49–90)	63 (39–71)	41 (39–43)	47 (37–57)	60 (19–78)	64 (19–90)
Alien limb side: left (%)	65	71	55	80	100	70	69
Median time from disease onset to alien limb in months	12 (0–96)	0 (0)	0 (0–3)	9 (0–48)	1(0–3)	0 (0–36)	6(0–96)
Neuropathology	3 AD, 1 CBD,	0	2	4	3	2	15

Range in parenthesis

CBS corticobasal syndrome, *CBD* corticobasal degeneration, *AD* Alzheimer's disease, CJD Creutzfeldt-Jakob Disease, *HDLS* Hereditary Diffuse Leukoencephalopathy with Spheroids

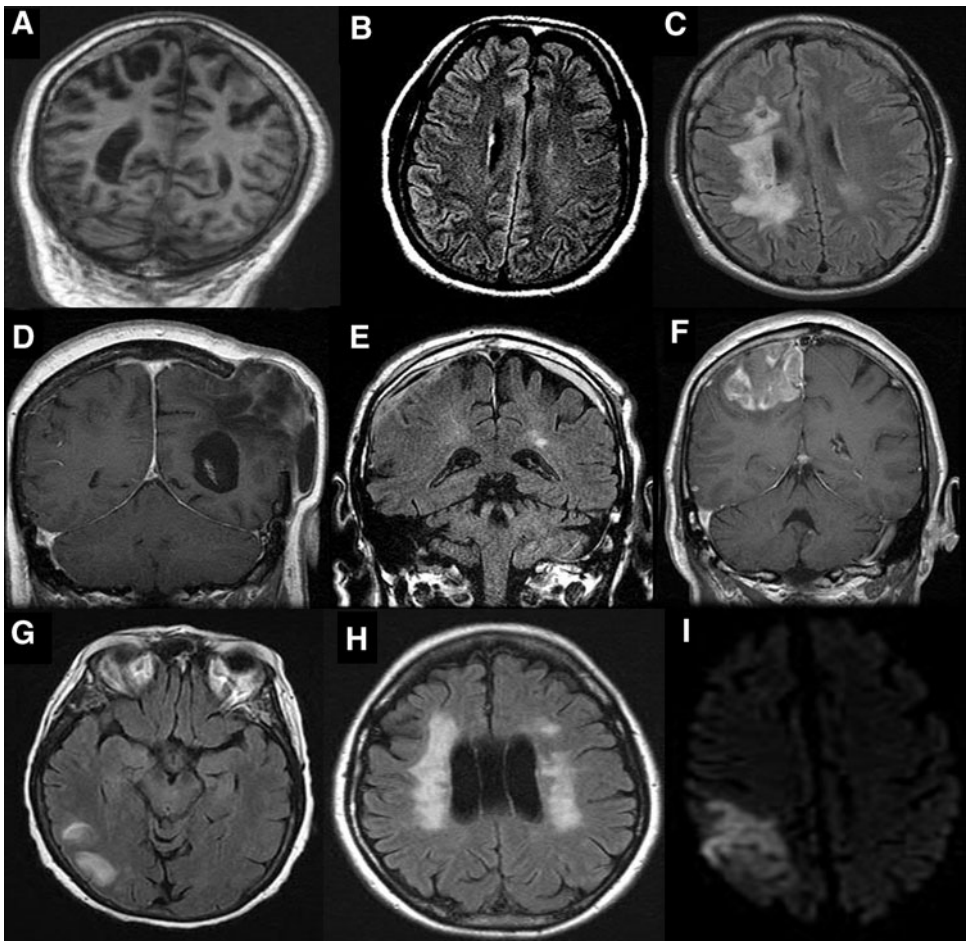

Fig. 2 Montage of select cases demonstrating radiographic changes associated with the alien limb among different pathological processes. The cases are described from *top* to *bottom*, from *left* to *right*; **a** coronal T-1 MRI demonstrating right parietal atrophy attributed to CBS, **b** axial T-2 weighted FLAIR sequence showing right hemispheric cortical ribboning associated with CJD, **c** T-2 weighted FLAIR sequence showing a large demyelinating lesion in the right posterior corona radiata in a demyelinating disorder not otherwise specified, **d** coronal T-1 waited sequence with prominent left parietal encephalomalacia associated with a now-resolved intracranial hemorrhage, **e** coronal T-2 weighted FLAIR sequence demonstrating bilateral subdural hematomata with subarachnoid hemorrhage and associated cortical irritation of the right parietal lobe, **f** coronal gadolinium-enhanced T-1 weighted sequence showing a right parietal tumor, **g** axial FLAIR image demonstrating characteristic changes of the posterior reversible encephalopathy syndrome, **h** axial FLAIR sequence demonstrating bilateral corona radiata abnormalities in hereditary diffuse leukodystrophy with axonal spheroids, **i** axial DWI demonstrating a right parietal infarct. In all cases, the alien limb was contralateral to the afflicted parietal lobe

versus 64.6 (9.04) without($p = 0.237$)). Fifty-five percent were female among those with alien limb versus 49 % without alien limb. Notably, the left limb was the affected side in 73 % ($n = 16$) of these 22 ADRC patients with alien limb. This contrasts with only five cases (23 %) affecting the right extremity; one case had both extremities affected simultaneously. Overall, the left side was the predominantly affected side in approximately half of the 44 CBS cases ($n = 23$); of these, 70 % ($n = 16$) developed an alien limb in contrast to only 24 % ($n = 5$) with right-limb-onset CBS. Left sided predominant CBS was significantly associated with the presence of alien limb phenomena ($p = 0.004$). The same percentage (95 %) of patients with and without alien limb had limb apraxia. Fifty-five percent of CBS patients with alien limb had dystonia compared to 50 % of patients without alien limb.

In the non-ADRC cohort, predominant left sided alien limb occurred in 65 %.

Neuropathology

Neuropathology was available in 17 cases. Table 1 includes the pathological diagnoses available for each clinical diagnosis. Two cases underwent brain biopsy without definitive diagnoses being made. Two of the brain tumors were grade 3 of 4 astrocytoma. One was an oligodendroglioma. In the "other" subgroup, one case was demyelinating, and the other was thalamic dementia

Table 2 Associated neurologic findings

	Etiology					
	CBS	Cerebrovascular	CJD	HDLS	Tumor	Total
Frontal/Callosal* (%)	7	0	0	20	0	7
Dystonia (%)	49	0	66	20	0	42
Cortical sensory findings[#] (%)	44	60	77	0	50	49
Rigidity (%)	94	20	88	100	25	81
Apraxia (%)	96	53	66	100	50	87
Neglect (%)	16	33	55	0	0	21
Mirror Movements (%)	41	0	0	20	0	31
Myoclonus (%)	32	0	88	20	0	31

CBS corticobasal syndrome, *CJD* Creutzfeldt-Jakob Disease, *HDLS* Hereditary Diffuse Leukoencephalopathy with Spheroids

* Frontal signs included pathologic grasp, palmomental sign, and utilization behavior. Intermanual conflict

[#] Cortical sensory findings included agraphesthesia and/or astereognosis

Table 3 Examples of alien limb phenomenon (from medical record)

CBS	The limb will involuntarily grab hold of her clothes. Her husband says when he is putting her clothes on that the right arm starts to move towards him to interfere. She does say "that damn arm" or "it" or "my friend" when referring to her arm
Stroke	She woke up in the morning and felt that there were extra hands and arms in her bed but when she looked it was her hands and arms. She also felt that she could not control her left arm which was grasping parts of her body
HDLS	Left upper extremity would "go whenever it wanted to." While walking through the mall, the left arm would grab on to his shirt or grab on to his hat involuntarily
CJD	She felt her left upper extremity and lower extremity were "not hers." Specifically, when she was undressing in the dark, her left upper extremity has swung over and hit her in the abdomen, and she was unable to tell that this was her arm; she thought it was someone else's. Also she would repeatedly ask her husband "whose leg is that", pointing to her own leg
PRES	She had wandering movements of her left arm which she said were involuntary. Throughout the exam, she looked at her hand with a sense of strangeness
Tumor	The patient also began noting difficulties with his left arm and he describes an alien limb with his hand wandering in space involuntarily
PML	He developed involuntary movements of left arm along with a sense of estrangement which resulted in trauma to the limb

characterized by thalamic and inferior olivary gliosis, absent neurofibrillary tangles and pretangles with no evidence of α-synuclein or prion protein deposits.

Discussion

This large cohort of patients with alien limb allows some generalizations regarding neuroanatomic substrates. Thus, focal lesions across all etiologies studied, even if multifocal, consistently affect the parietal lobe contralateral to the alien limb. Moreover, right hemisphere damage is more likely than left to be associated with alien limb. In addition, diseases predominantly affecting white matter, including HDLS, progressive multifocal leukoencephalopathy, posterior reversible leukoencephalopathy syndrome, may exhibit this phenomenon. These findings are consistent with the proposal that alien limb phenomena are at least partially related to white matter damage underlying the right parietal cortex, disconnecting it from other cortical areas of the brain such as the contralateral hemisphere or motor areas in the same hemisphere. This would allow for misperception by the other hemisphere, causing descriptions such as in Table 3, loss of awareness of the arm moving, and loss of sensory input from motor cortex when the arm moves.

Although CBS is most frequently associated with alien limb (108 of 150 cases), the differential diagnosis includes a variety of other less common conditions, including CJD (nine patients) and HDLS (five patients). Furthermore, alien limb phenomena were seen with demyelinating disease, progressive multifocal leukoencephalopathy, and the posterior reversible encephalopathy syndrome.

The timing of the alien limb in the course of the disease can help distinguish amongst the various etiologies. We have previously reported that when alien limb occurs in

Table 4 Location of stroke and tumor in alien limb cases

Case	Cause	Imaging
1	Ischemic stroke, cardioembolic	MRI brain: Left inferior parietal/posterior temporal region
2	Ischemic stroke, cryptogenic	MRI brain: Acute infarct in the right frontal operculum and in the anterior right parietal lobe, with restricted diffusion
3	Ischemic stroke, cardioembolic	MRI brain: Wedge-shaped zone of restricted diffusion involving the anterior right parietal lobe including portions of the post central gyrus
4	Ischemic stroke, procoagulant state	MRI brain: Partially enhancing recent infarct of the right post central gyrus as and recent small cortical infarct in the deep portion of the post central sulcus. Patchy infarcts left occipital-parietal lobes with mild evolution superomedially
5	Ischemic stroke, right carotid artery disease	MRI brain: Subacute wedge-shaped infarct in the right posterior frontal parietal region and smaller areas of infarction in the right frontal cortex including the boundary zone between the anterior and middle cerebral artery distributions
6	Ischemic stroke, cryptogenic	MRI brain: T2 hyperintensity within the medial right parietal occipital lobe with minimal linear enhancement following contrast administration
7	Ischemic stroke, carotid artery disease	MRI brain: Large area of restricted diffusion within the left parietal lobe
8	Ischemic stroke, cardioembolic	MRI brain: Acute infarct involving the superior left parietal lobule, with additional small focus of acute infarction in the subcortical white matter of the left occipital lobe. Additional chronic punctate infarcts within the right thalamus, bilateral basal ganglia, and left occipital white matter
9	Arteriovenous malformation	MRI brain: 3.0 cm arteriovenous malformation located in the anterior right parietal lobe, which abuts the posterior margin of the post central gyrus on the right
10	Ischemic stroke from carotid stenosis	MRI brain: Right parietal lobe
11	Ischemic stroke, cardioembolic	MRI brain: Acute infarction with restricted diffusion in the right superior temporal-parietal lobe and the posterior right insula. Two additional focal zones of increased T2 signal and restricted diffusion in the right cerebellar hemisphere
12	Ischemic stroke, cryptogenic	MRI brain: Large area of encephalomalacia involving the mesial left temporal and adjacent occipital lobe which extends into the left calcarine cortex. There are smaller infarcts in the callosal splenium, both dorsal thalami, left posterior corona radiata, and right superior cerebellum
13	Subdural hematoma	MRI brain: Bilateral chronic subdural hematomas with recent re-hemorrhage in the right frontal region. Increased T2 signal within the cortex of the right posterior frontal and parietal regions
14	Astrocytoma	MRI brain: Heterogeneously-enhancing mass lesion in the right parietal lobe with minimal focal associated mass effect, enhancing T2 hyperintensity and expansion of the right thalamus, and a small focus of enhancing T2 hyperintensity involving the medial right hypothalamus. Also with increased nonenhancing T2 hyperintensity involving the anteromedial right temporal lobe
15	Astrocytoma	MRI brain: Nonenhancing diffuse infiltrative T2 hyperintensity extending inferiorly from the pre- and postcentral gyrus bilaterally through the centrum semiovale which extends across an enlarged body and splenium of the corpus callosum where there is a nodular foci of restricted diffusion extending to the posterior body the right ventricle
16	Oligodendroglioma	MRI brain: There is a cortical and subcortical mass in the right mid to posterior frontal lobe, near the vertex extending into the parietal lobe
17	Astrocytoma	MRI brain: Multifocal high T2 signal lesions with enhancement within the right parietal lobe, right thalamic body and right hypothalamic region. The largest of these lesions is within the right parietal lobe, measuring approximately 5.0 cm with surrounding region of increased T2 signal edema, right cerebral hemispheric mass effect and slight right to left shift of midline with effacement of the occipital horn of the right lateral ventricle

Note Imaging or outside reports available for 13/14 of the cerebrovascular cases

CJD it is often the initial neurological sign prompting medical evaluation [37]. In contrast, when alien limb typically occurs in CBS or HDLS, the presentation occurs nearly 1 year into disease onset.

Associated findings are often helpful in the differential diagnosis. The alien limb of CBS occurred commonly with rigidity, apraxia or other key features. Mirror movements, albeit uncommon, suggested CBS and less likely HDLS. Myoclonus occurred in most cases of CJD-related alien limb and never occurred in stroke (e.g., the only other cause of rapid onset alien limb). Intermanual conflict (one hand directly opposes the action of the other) was not common in our patient cohort, documented in only 7 % of CBS cases. Also, note that alien limb rarely occurs, in the absence of other neurologic signs, especially in CBS and later-stage CJD (see Table 2). The constellation of signs do not appear

particularly specific to a mechanism and conform to findings in each disease without the alien limb. Accumulation of neurologic signs might be more suggestive of the fulminant pathology of CJD, especially if myoclonus is present.

The right hemisphere as the substrate for the alien limb was a prominent finding in our cohort, consistent across neurodegenerative and lesional causes. This predominance is substantially different from the aforementioned older series; reasons for the difference likely include the large number of cases of CBS and the infrequency of callosal surgeries currently performed for seizure control. Thus, in 69 % of our cases the left limb was predominately affected as part of the alien limb syndrome. In the ADRC CBS cohort, in which alien limb was most carefully documented, the left limb was involved 73 % of the time. While CBS appears to occur equally in either hemisphere, alien limb occurs more frequently with left limb (e.g., right hemisphere) onset CBS. The reason for the right hemisphere, left limb predominance is unclear. Perhaps, the right hemisphere involvement predisposes to the sense of estrangement from the limb akin to a neglect phenomenon. Consistent with our results, diffusion tensor imaging in CBS has demonstrated a reduction in the sensorimotor fibers of the hand cortical representations [8].

Although alien limb is a helpful diagnostic marker of CBS, it was present in only half of our 44 ADRC CBS cases. This frequency is similar to one other large clinical CBS series of referral center patients, where the prevalence in CBS was about 42 % [28]. Of note, alien limb occurs more often than dystonia CBS which has been reported to occur in 37.5 % of patients with corticobasal degeneration which is the prototypical pathological entity underlying CBS [39].

We and others have previously demonstrated that CBS is associated with a spectrum of underlying neurodegenerative disorders, and; hence, CBS is not an accurate predictor of underlying corticobasal degeneration pathology [6]. Furthermore, cortical or corpus callosum atrophy, or subcortical and periventricular white matter signal changes on MRI, are not specific to CBD [25]. The clinicopathologic findings in this report also demonstrate that alien limb in CBS cases does not accurately predict underlying CBD neuropathology.

Our series has several limitations. The study was retrospective, which was necessary given the rarity of the disorder. The predominance of the so-called posterior phenotype seen in our series precludes us from comparing the anatomy and features of the other alien limb phenotypes to the posterior phenotype. While the limited number of cases of anterior alien limb is a limitation of the study, the large number of posterior variant alien limb cases described highlight the predominance of this variant in clinical practice.

Conclusions

The alien limb is caused by heterogenous pathologies. This emphasizes the role of affected topography and not necessarily the pathology in determining the presence of alien limb. The CBS, stroke and CJD are the most likely etiologies. It is most often associated with right hemisphere, left hemibody involvement. Given the increased awareness of CBS and decline of callosotomy surgeries, the posterior sensory alien limb has become the most prevalent subtype.

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Conflicts of interest The authors declare that they have no conflict of interest.

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