Isolated Insular Stroke: Clinical Presentation

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Abstract

The symptoms related to insular ischemia have been the object of several studies in patients affected by stroke, although they are often accompanied by other ischemic alteration of adjacent brain structures supplied by the middle cerebral artery (MCA). The insula is vulnerable because of an ischemia due to thromboembolic vascular occlusion of the M1 MCA segment and the 2 main MCA branches (M2), mainly when they abruptly arise from the principal stem at a right angle. This topographical and anatomical peculiarity could enable an embolic formation, especially due to atrial fibrillation (AF), to occlude the transition pathway between M1 and M2, while the proximal origin of vascular supply protects the insula from ischemia due to hemodynamic factors. The aim of the study is to characterize the clinical aspects of acute ischemic strokes as a first event in the insular territory with specific attention to atypical manifestation. We have considered 233 patients with a first event stroke involving the insular territory and 13 cases of isolated insular stroke (IIS), from the stroke registry of the Policlinico “G.Martino”, University of Messina, between the February 10, 2014 and the February 7, 2018. IIS patients showed CT/MRI lesions restricted to the insular region. Exclusion criteria were coexisting neurological diseases, structural brain lesions, extension to the subinsular area > 50% of the total infarct volume. We identified 13 IIS patients (mean age 74 years), with an isolated symptom or a combination of typical and atypical aspects. Furthermore, we observed high frequency detection of cardiac disturbances. To our knowledge, just a few previous studies have described IIS; their incidence is still not well defined. IIS manifested with a combination of deficits including motor, somatosensory, speaking, coordination, autonomic and cognitive disturbances. After an ischemic stroke, AF manifestation could follow briefly the major event and its duration could be very short, as an autonomic dysfunction due to an insular infarction. This clinical condition requires a continuous cardiac monitoring for this dangerous occurrence.

Introduction

The human insular cortex (IC) is a complex structure that has been implicated in a large number of functions and in the pathophysiology of a variety of neurologic disorders [1].
From the cytoarchitectural, connectivity, and functional standpoint, it is subdivided into dorsocaudal and rostroventral zones. The dorsocaudal (granular) zone comprises several areas that receive inputs from different subnuclei of the thalamus that relay gustatory, viscerosensory, somatosensory, pain, and vestibular sensations. The rostroventral (agranular) zone is interconnected with the anterior cingulate cortex and the amygdala and is primarily involved in emotional processing. The terms agranular and granular refer to the absence or presence of an internal granular layer (IV). There is a wide intermediate zone, termed dysgranular because granule cells are rather scarce in layer IV and do not display complete laminar differentiation.

It appears that in monkeys, the superior tier of the insula contains 4 anteroposteriorly arranged primary sensory areas; gustatory, general viscerosensory, somatosensory (pain and temperature), and vestibular. According to the neuroanatomical studies in rhesus macaques (Fig. 1), the IC:

− receives afferents from the dorsal thalamus (ventral posterior superior nucleus, ventral posterior inferior nucleus, ventromedial posterior nucleus, parvocellular part of the ventral posteromedial nucleus) and from several sensory cortical areas. In particular, the afferents from olfactory prepiriform cortex, the primary and secondary gustatory cortices and the primary insular viscerosensory cortex converge on the agranular anterior zone of the insula, which participates with the caudal orbitofrontal cortex in the formation of an “orbital network”, involved in the analysis and integration of food-related information. Afferents from the primary somatosensory cortex, the somatosensory association areas 5 and 7b, the primary vestibular areas 3a and 2v, as well as from the auditory association areas, surrounding the primary auditory cortex, project to the posterosuperior portion of the insula (parieto-insular vestibular cortex; insular nociceptive and thermoreceptive cortex) and converge on the area which may hence be characterized as the insular somatic association cortex.

− is reciprocally connected with the amygdala as well as with several limbic and association cortical areas. Limbic structures, including the entorhinal (area 28), perirhinal (areas 35, 36), posterior orbitofrontal (areas 13, 14), temporopolar (area 38), and cingulate (areas 23, 24) cortices, as well as the amygdaloid complex, are strongly and reciprocally connected with the anterobasal sector of the insula, the insular limbic cortex. The insular somatic association cortex and the insular limbic cortex represent way stations in a somatolimbic projection, may provide a means for interrelating events in the extrapersonal world with relevant motivational states. Some high-order association areas, including the anterior orbitofrontal cortex (area 11), the prefrontal cortex (areas 45, 46), and the polymodal association cortex occupying the banks of the superior temporal sulcus, are also known to be connected with the insula.

− projects to the supplementary and presupplementary motor areas forming part of the medial premotor cortex, as well as to the ventral and dorsal striatum.

− moreover, there is an abundance of local intrainsular connections.

In humans, the posterior insular cortex (PIC), middle insular cortex, and anterior insular cortex (AIC) sectors of the insula represent 3 different stages or levels of integration in a posteriorly-to-anteriorly directed processing stream. Afferents from the solitary nucleus, and from the phylogenetically new pathway from lamina I spinal neurons, converge upon the PIC, where they provide a primary interoceptive representation of the physiological condition of the body. The middle insular cortex is to be considered a polymodal integrative zone, where the interoceptive information from the posterior insula is represented and associated with inputs from multiple other sources. Prominent among these are

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The insula is supplied directly by the proximal portions of the 2 main branches of the MCA (M2), where they abruptly arise from the main stem (M1) at a right angle. This topographical and anatomical characteristic of the insula could enable an embolism, especially an atrial fibrillation (AF), to occlude in the transition region between the M1 and M2. The insula is vulnerable to ischemia due to thromboembolic vascular occlusion of the M1 MCA segment and the superior and inferior MCA trunks, because no possibility exists of pial collateral supply from the anterior or posterior cerebral arteries [9]. However, the proximal origin of vascular supply protects the insula from ischemia due to hemodynamic factors in the absence of thromboembolic occlusion. Insular involvement might be highly associated with the specific pathomechanism of ischemic stroke [8].

The IC plays an important role in the regulation of the autonomic nervous system. Electrical stimulation of the left IC more frequently elicited a small decrease in heart rate (HR) and blood pressure, whereas stimulation of the right IC elicited the opposite effects [10]. This has led to the suggestion that the left IC primarily regulates the parasympathetic and the right IC the sympathetic influence on the heart [11]. This appears to be supported by fMRI studies showing a correlation between left IC activation and high frequency (vagal) modulation of HR variability [12], and lateralization of insular activation during the Valsalva maneuver, cold pressor test, and handgrip maneuver [13]. However, this may be an oversimplification. For example, concomitant fMRI and microelectrode recordings show that resting muscle sympathetic nerve activity coincides with activation of the left IC, whereas skin sympathetic activity coincides with activation of the left posterior and right anterior insula [14].

To isolate insular symptoms it would be interesting to analyze the clinical consequences of the rare ischemic strokes limited to the insula. The aim of the study is to characterize the clinical aspects of acute ischemic strokes as a first event in the insular territory with specific attention to atypical manifestation.

Materials and Methods

We have considered 233 patients with a first event stroke involving the insular territory and 13 cases of IIS, from the stroke registry of the Policlinico “G.Martino”, University of Messina, between the February 10, 2014 and the February 7, 2018. We reviewed medical charts and neuroimaging studies of the last 723 patients of each database with MCA stroke. Those with infarcts predominantly affecting the IC were eligible. IIS patients showed CT/MRI lesions restricted to the insular region. Extension to the adjacent operculae or subinsular area (extreme capsule, claustrum, external capsule) was accepted as long as it accounted for <50% of the total infarct volume. Exclusion criteria were coexisting neurological diseases, structural brain lesions, extension to the subinsular area >50% of the total infarct volume.

Intravenous thrombolysis (IVT) with tissue-type plasminogen activator (rT-PA) was administered to eligible patients, according to Guidelines for Thrombolytic Therapy [15]. Therapeutic approaches included direct mechanical thrombectomy (MT) or bridging therapy with rT-PA plus MT. Collected data included patient demographic and clinical characteristics, time of symptoms onset, initial stroke severity as expressed by the National Institutes of Health Stroke Scale score on admission and discharge, and the modified Ranking Scale on admission and discharge [15].
Results

We identified 13 IIS patients (5 males, 8 females), with a mean age of 74 years (range, 47–90), divided as right IS and left IS depending on the hemisphere involved (Fig. 2–5). IIS patients presented with an isolated symptom or a combination of typical – motor deficits (13/13 – 4 right, 9 left), sensory impairment (6/13 – 2 right, 4 left), speech disorder (11/13 – 3 right, 8 left) – and atypical aspects – hemispatial inattention (2/13 – 2 right), sleepiness (2/13 – 2 right), vestibular-like syndrome (5/13 – 3 left, 2 right), auditory disturbance (1/13 – 1 left), transient dysphagia (3/13 – 3 left), space-time disorientation (1/13 – 1 right), confusion and agitation (1/13 – 1 left), weeping tendency (1/13 – 1 left) and anxiety (1/13 – 1 right), autonomic disturbance (11/13 – 8 left, 3 right; Table 1 and Fig. 6).

Somatosensory manifestations were reported in 13 patients (100%). Symptoms included numbness ($n = 4$) and dysesthesia ($n = 2$). The deficit was contralateral to the lesion in all cases. It affected a hemibody with ($n = 1$) or without facial sparing ($n = 9$), or was limited to facial territory and omolateral arm ($n = 3$).

Aphasia was reported in 6 patients (46%). Non-fluent aphasia with anomia and phonemic paraphasia was the most frequently reported clinical picture ($n = 5$). Wernicke’s aphasia ($n = 1$) was also reported.

Dysarthria ($n = 5, 38\%$) and a vestibular-like syndrome variably described as vertigo, dizziness, unsteadiness or instability ($n = 5, 38\%$) were also frequently reported. Hemispatial inattention ($n = 2$), sleepiness ($n = 2$), auditory disturbance ($n = 1$), transient dysphagia ($n = 3$), space-time disorientation ($n = 1$), confusion and agitation ($n = 1$), weeping tendency ($n = 1$) and anxiety ($n = 1$) were rarely reported.

Dysautonomic disorders were also frequently reported ($n = 11, 85\%$), characterized by hypertension bursts ($n = 6$), hypotensive/hypertensive episodes ($n = 4$), and cardiac rhythm disturbances ($n = 9$).

Furthermore, we observed high frequency detection of cardiac involvement ($n = 11, 85\%$): history of tachycardia ($n = 1$) or AF (permanent, $n = 2$; paroxistic, $n = 2$), newly detected ($n = 2$) or suspected AF (biantial enlargement on transthoracic echocardiogram, $n = 2$), atrial flutter ($n = 2$), sinus bradycardia ($n = 1$) or tachycardia ($n = 1$), atrioventricular blocks (complete or incomplete left/right branch block, QT prolongation, atrioventricular block, $n = 6$) and an increased ectopic beats ($n = 2$; Fig. 7).

IVT with rT-PA was performed, at the standard dose of 0.9 mg/kg, for 8 patients. Within this group, 2 patients...
out of 8 underwent MT in a setting of bridging therapy. Five patients did not receive IVT with rT-PA: within this group, 1 patient underwent direct MT to perform right carotid angioplasty and stenting; 1 patient underwent MT alone because of the presence of early ischemic signs on CT scan; 3 patient did not perform IVT because of rapid regression of symptoms, late hospital arrival (outside time window for IVT) or because of the presence of high microbleed counts on MRI. Table 2 shows the summary results for reperfusive treatments with National Institutes of Health Stroke Scale on admission and discharge and modified Ranking Scale before and after the hospitalization.

Discussion/Conclusion

IIS were described only in few previous studies or case reports and their incidence is not well defined. Due to the confluence of functions in a restricted region, IIS results in multimodal deficits combining in descending order motor and somatosensory, speech or language, vestibular-like, autonomic and cognitive disturbances [7].

Although motor and sensory deficits, aphasia and dysarthria are among the well-known, described symptoms of IS, in accordance with literature, we observed many unusual clinical presentations, such as vestibular-like syndrome, auditory disturbances, hemispatial inattention, cognitive alterations, and autonomic dysfunction.

Neurons in the parieto-insular vestibular cortex respond to vestibular stimuli; further, most of these elements also responded to somatosensory and visual information and were hence, classified as polymodal vestibular units. In humans, a vestibular cortical network with right hemispheric dominance comprises, among many other cortical areas, the PIC as well as the AIC [16]. In contrast to these observations, however, we did not find a side preference for vestibular-like syndrome.

The PIC is involved in auditory processing, such as tuning into novel auditory stimuli and allocating auditory attention [17]. This could explain the singular finding of acute auditory disturbance.

Some patients with hemiplegia after right-sided strokes deny their paralysis (anosognosia for hemiplegia) and are convinced that their paralyzed limbs function normally or they may experience their limb(s) as not belonging to them and may even attribute them to other persons (somato-
paraphrenia). The disturbances are consistently associated with damage to the right insula, suggesting a prominent role of the right insula in our sense of limb ownership as well as in our self-awareness of actions. Hence, Karnath and Baier hypothesized that the right IC forms a central node of the network involved in human body scheme representation [18]. In accordance with this observation, we found 2 cases of left hemineglect in patient with right IIS.

The AIC is involved in a large variety of cognitive control tasks. This insular region forms, together with other cortical regions, among which the anterior cingulate cortex, the presupplementary motor area, the dorsal premotor cortex, the dorsolateral prefrontal cortex, and the posterior parietal cortex, a highly interconnected cognitive control network [19]. The frontoinsular cortex is a cytoarchitecturally distinct anterior subdivision of ventral AI, and right frontoinsular has been proposed as the central node within a large-scale “salience network” that responds to personally significant ambient events. In contrast to the ventral anterior insula, which participates in social-emotional function, the dorsal anterior insula has been strongly linked to cognition [20]. Sterzer et al. [21] demonstrated that gray matter volume in bilateral AIC and left amygdala was significantly reduced in Conduct Disorder patients, compared to healthy control subjects. According to the authors mentioned, these findings sug-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Topography</th>
<th>Typical symptoms</th>
<th>Atypical symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63, male</td>
<td>Right</td>
<td>Left hemiparesis, dysarthria</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>76, female</td>
<td>Left</td>
<td>Right hemiparesis, non-fluent aphasia, right tactile extinction</td>
<td>Vestibularlike syndrome, newly-detected AF, incomplete LBB and hypertensive episode</td>
</tr>
<tr>
<td>3</td>
<td>70, male</td>
<td>Left</td>
<td>Right facial and arm weakness, non-fluent aphasia</td>
<td>Transient dysphagia, vestibularlike syndrome, hypotensive/hypertensive episodes</td>
</tr>
<tr>
<td>4</td>
<td>68, male</td>
<td>Right</td>
<td>Left hemiplegia, left arm hypoesthesia, mild dysarthria</td>
<td>Sleepness, left hemineglect, hypotensive/hypertensive episodes</td>
</tr>
<tr>
<td>5</td>
<td>84, male</td>
<td>Right</td>
<td>Left hemiparesis</td>
<td>Sleepness, space-time disorientation, left hemineglect, vestibularlike syndrome, atypical atrial flutter and hypertensive episode</td>
</tr>
<tr>
<td>6</td>
<td>90, female</td>
<td>Left</td>
<td>Right hemiparesis, non-fluent aphasia</td>
<td>Atypical atrial flutter, hypertensive episode and bradicardic episode</td>
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<tr>
<td>7</td>
<td>47, female</td>
<td>Right</td>
<td>Left hemiparesis, right limbs pain, dysarthria</td>
<td>Anxiety, transient dysphagia, vestibularlike syndrome, hypotensive/hypertensive episodes and sinus tachycardia</td>
</tr>
<tr>
<td>8</td>
<td>74, female</td>
<td>Left</td>
<td>Right facial and arm weakness, right arm pain</td>
<td>Sinus bradycardia, atrial extrastyslote and hypertensive episode</td>
</tr>
<tr>
<td>9</td>
<td>85, female</td>
<td>Left</td>
<td>Right hemiparesis, non-fluent aphasia</td>
<td>Transient dysphagia, constipation, newly detected AF, sinus bradycardia with AVB I and RBB, hypertensive episode</td>
</tr>
<tr>
<td>10</td>
<td>71, male</td>
<td>Left</td>
<td>Right hemiparesis, non-fluent aphasia</td>
<td>Weeping tendency, ectopic ventricular beats and hypertensive episode</td>
</tr>
<tr>
<td>11</td>
<td>69, female</td>
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<td>Right facial and arm weakness, dysarthria</td>
<td>Hypertensive episode</td>
</tr>
<tr>
<td>12</td>
<td>81, female</td>
<td>Left</td>
<td>Right hemiparesis, right hemihypoesthesia, fluent aphasia</td>
<td>Confusion, agitation, auditory disturbance, delayed RB conduction</td>
</tr>
<tr>
<td>13</td>
<td>88, female</td>
<td>Left</td>
<td>Right limbs weakness, right hemihypoesthesia, mild dysarthria</td>
<td>Vestibularlike syndrome, RBB and hypotensive/hypertensive episodes</td>
</tr>
</tbody>
</table>

IIS, isolated insular stroke; AF, atrial fibrillation.

Table 1. Clinical presentation in patients with IIS
Fig. 6. Frequency of typical and atypical symptoms.

Fig. 7. Cardiac involvement in patients with IIS. AF, atrial fibrillation.

Table 2. Summary results for reperfusive treatments with NIHSS on admission and discharge and mRS before and after the hospitalization

<table>
<thead>
<tr>
<th>Patient</th>
<th>IVT</th>
<th>MT</th>
<th>NIHSS (admission)</th>
<th>NIHSS (discharge)</th>
<th>Premorbid mRS</th>
<th>Discharge mRS</th>
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<tr>
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<td>Y</td>
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<td>1</td>
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<tr>
<td>2</td>
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<td>N</td>
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<tr>
<td>3</td>
<td>N</td>
<td>Y</td>
<td>9</td>
<td>6</td>
<td>1</td>
<td>4</td>
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<tr>
<td>4</td>
<td>N</td>
<td>Y</td>
<td>16</td>
<td>3</td>
<td>0</td>
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<tr>
<td>5</td>
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<td>Y</td>
<td>13</td>
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<td>0</td>
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<tr>
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<td>N</td>
<td>14</td>
<td>12</td>
<td>0</td>
<td>4</td>
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<tr>
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<td>N</td>
<td>N</td>
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<tr>
<td>8</td>
<td>N</td>
<td>N</td>
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<td>1</td>
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<tr>
<td>9</td>
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<tr>
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<td>11</td>
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<tr>
<td>11</td>
<td>Y</td>
<td>N</td>
<td>3</td>
<td>0</td>
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</tbody>
</table>

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Ranking Scale; IVT, intravenous thrombolysis; MT, mechanical thrombectomy.
gest a critical role for the AIC in regulating social behavior. These observations could explain our findings of alterations in space-time orientation, level of consciousness, behavior, mood and stress response.

The insula is shown to play a role in swallowing, due to the evidence that a lesion in the IC produces profound dysphagia. Some studies have revealed the bilateral involvement of the insula, while other researchers have reported the activation of the right insula during swallowing. There is also some evidence about the presence of anterior insula engagement in dysphagic patients and the interaction of insula as a modulator of motor function with primary sensory cortex lead to control of swallowing [22]. Swallowing disorder after stroke shows a spontaneous recovery and these observations are in accordance with our findings.

The insula plays a role in autonomic regulation. Electrical stimulation of the insular region in humans may elicit a variety of visceromotor phenomena, including vomiting and other alterations of the gastrointestinal tract, respiratory arrest, as well as changes in cardiac rate and rhythm control, and blood pressure [10, 23].

Central autonomic disorders may manifest with a wide spectrum of cardiac arrhythmias, some of them life-threatening. Sympathetic hyperactivity triggers both supraventricular and ventricular tachycardia; vagal hyperactivity leads to bradyarrhythmias, including AV block, and sympathetic or vagal hyperactivity may lead to AF. Reduced HR variability is a relevant marker of cardiovascular risk, including predisposition toward ventricular arrhythmias in patients with primary cardiac disease. They may reflect abnormalities in forebrain vagal or sympathetic drive, brainstem reflexes, or vagal or sympathetic output [24].

AF detected after acute ischemic stroke may be short-lasting and perhaps a nonrecurrent autonomic and inflammatory epiphenomena of stroke. The autonomic regulation of cardiac rhythm constitutes an integrated relay system. The highest level of control is exerted by the cerebral cortex, particularly the insula. The onset of AF may be associated with an imbalance of sympathetic and parasympathetic activity, a common consequence of insular infarctions. This autonomic imbalance and an interruption in the cerebral regulation of the intrinsic cardiac autonomic system constitute the most likely mechanisms responsible for the autonomic pathway. Insular damage has been associated with newly detected AF, atrioventricular blocks and an increased amount of ectopic beats. Furthermore, insular damage is associated with adverse cardiac outcome, such as sudden cardiac death and congestive heart failure [25]. Early and accurate identification of stroke patients at high risk for AF is important in selecting candidates for intensive cardiac monitoring such as implantable loop recorders. Larger studies are needed to better define the incidence and clinical presentation in IIS [26].

To our knowledge, just a few previous studies have described IIS; their incidence is still not well defined [7]. IIS manifested with a combination of deficits including motor, somatosensory, speaking, coordination, autonomic and cognitive disturbances. After an ischemic stroke, AF manifestation could follow briefly the major event and its duration could be very short, as an autonomic dysfunction due to an insular infarction. This clinical condition requires a continuous cardiac monitoring for this dangerous occurrence.

### Limitations

It is a small study on clinical aspects of IISs from a prospective registry.

### Acknowledgment

We acknowledge the territorial emergency medical service, which has contributed in an essential way in carrying out the centralization system.

### Statement of Ethics

Subjects (or their parents or guardians) have given their written informed consent. The study protocol has been approved by the research institute’s committee on human research.

### Disclosure Statement

The authors have no conflicts of interest to disclose.

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This study did not receive any funding.

### Author Contributions

F. Giammello, D.C., C.C., and R.F.M. contributed to the study design. F. Giammello and D.C. performed data collections. F. Granata performed imaging analysis. M.C.F., M.C., P.L.S. supervised the research. F.Gi, F.Grillo, C.C., C.D.A. and R.F.M. wrote the article. A.T. supervised the submission of reviewed manuscript.
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