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MINI-REVIEW

The ventricular-subventricular, subgranular and subcallosal zones: three niches of neural stem cells in the postnatal brain

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Abstract

In the postnatal brain, three regions show high mitotic activity. These brain areas are neurogenic niches, and each niche harbors a microenvironment favorable for the proliferation and differentiation of neural stem cells. These multipotential cells maintain the capacity to self-renew and generate intermediate precursors that will differentiate into neuronal and glial lineages (astrocytes and oligodendrocytes). The most well-studied niches are the ventricular-subventricular zone (V-SVZ) of the lateral ventricles, the subgranular zone (SGZ) of the dentate gyrus in the hippocampus, and the subcallosal zone (SCZ), located in the limit between the corpus callosum and the hippocampal formation. The discovery of these three neurogenic niches has gained much interest in the field because they may be a therapeutic alternative in neural regeneration and neurodegenerative disorders. In this review, we describe in brief all these regions and explain their potential impact on solving some neurological conditions.

Keywords Neural stem cells · Neural precursors · Adult neurogenesis · Oligodendrocyte precursor cells

Introduction

From the first descriptions made by Altman (1962) referring to the birth of neurons in the adult mammalian brain to subsequent studies that demonstrate the presence of multipotential neural stem cells that generate in vivo neurons and oligodendrocytes in specific neural niches (Kriegstein and Alvarez-Buylla 2009), the study and manipulation of endogenous neural progenitors have generated a growing interest in regenerative medicine to fight against neurodegenerative disorders. However, plenty of questions remain to be elucidated about the mechanisms that regulate the proliferation, differentiation, function, and self-renewal of these multipotential neuronal cells, as well as the design of the appropriate techniques for their manipulation both in vitro and in vivo.

In mammals, including non-human and human primates, two of the adult brain's most studied neurogenic regions are the ventricular-subventricular zone (V-SVZ) and the subgranular zone (SGZ). The V-SVZ is located along the lateral ventricles as a thin layer that lies between the ventricular space and the brain parenchyma, whereas the SGZ is located between the hilus and the granular layer of the dentate gyrus within the hippocampal formation (Obernier and Alvarez-Buylla 2019). Most recently, a third proliferative niche, the subcallosal zone (SCZ), has been described and consists of small islets located between the corpus callosum and the CA1 and CA2 regions of the hippocampus (Seri et al. 2006; Kim et al. 2016). Adult neural stem cells have been isolated and purified in these three regions. These cells retain their astrocytic characteristics and multipotentiality that, in addition to self-renewal, give rise to precursors that differentiate into the main neural cell lines (Doetsch et al. 1999; Menn et al. 2006; Seri et al. 2006). These characteristics are preserved because the precursor cells are immersed in a microenvironment that provides the necessary nutrients and signals to keep them in a quiescent state and regulate their proliferation. Several elements of the extracellular matrix,

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cerebrospinal fluid, vascular system, etc. have been involved in this process (Li and Guo 2020). In the adult human brain, these three regions have also been described, but to date, only from the V-SVZ and SGZ has it been possible to isolate neural stem cells (Eriksson et al. 1998; Gonçalves et al. 2016) and there is currently no study that has described the isolation of neural stem cells in the human SCZ.

Under experimental conditions, neural progenitor cells obtained from these regions have been used in experimental protocols to generate new therapeutic alternatives for degenerative processes in the central nervous system (CNS), such as cerebral ischemia, multiple sclerosis, Alzheimer's disease, and Parkinson's disease, among others. Therefore, a crucial element to achieving the manipulation and isolation of neural stem cells is the knowledge of the cytoarchitectural organization and the molecular signals involved in regulating brain germinal niches. Herein, we describe the cellular composition and anatomical location of the three niches in the postnatal brain of rodents. Although we also described some findings discovered in the human brain.

The ventricular-subventricular zone (V-SVZ) of the lateral ventricles

The V-SVZ is a thin layer located adjacent to the walls of the lateral ventricles of the brain (Doetsch et al. 1997; García-Verdugo et al. 1998), which is the main adult neurogenic region in the adult brain (Alvarez-Buylla and Garcia-Verdugo 2002). This region derives from the ventricular zone (VZ), which also originates the ganglionic eminences during embryonic development. Thus, the adult V-SVZ contains multipotential cells that share functional and biochemical properties with the neuroepithelium (García-Verdugo et al. 1998). The cytoarchitecture of V-SVZ is composed of ependymal cells (type-E cells) that form a layer that delimits the parenchyma of the ventricular cavity (Fig. 1). Two types of ependymal cells have been described: type E1 and type E2. Type E1 cells have multiple cilia in the ventricular space, and their beating establishes the movement of the cerebrospinal fluid. Ependymal cells also serve as a "cellular filter" for brain molecules and facilitate the dispersion of neural messengers. Type E2 cells have an elongated basal body with one or two cilia, comprise around 5% of the cell population, and have been involved in controlling the proliferative stage of neural precursors (Mirzadeh et al. 2008).

Beneath the layer of type E cells, other precursors called type-B cells are distributed in the V-SVZ. Two subtypes of type-B cells have been described in this region: type-B1 and type-B2 cells (Doetsch and Alvarez-Buylla 1996). This categorization is based on the functional properties and molecular markers of these cells. Hence, type-B1 cells, which express radial-glia cell markers, are known as the neural stem cells of V-SVZ (Fig. 1), whereas the cells that express typical astrocytic markers are classified as type-B2 cells (Morshead et al. 1994; Doetsch et al. 1999). Type-B1 cells give rise to rapidly dividing cells known as transit amplifying cells, or type-C cells, which are in close contact with the chains of migrating neuroblasts (Cebrian-Silla et al. 2021) and local blood vessels (Snapyan et al. 2009; Fujioka et al. 2019). Some proteins that regulate the function of type-B1 and type-C cells throughout this neurogenic process include epidermal growth factor (EGF), insulin-like growth factor 2 (IGF-2) (Lim and Alvarez-Buylla 2016), neuroglobin (Haines et al. 2013), among others.

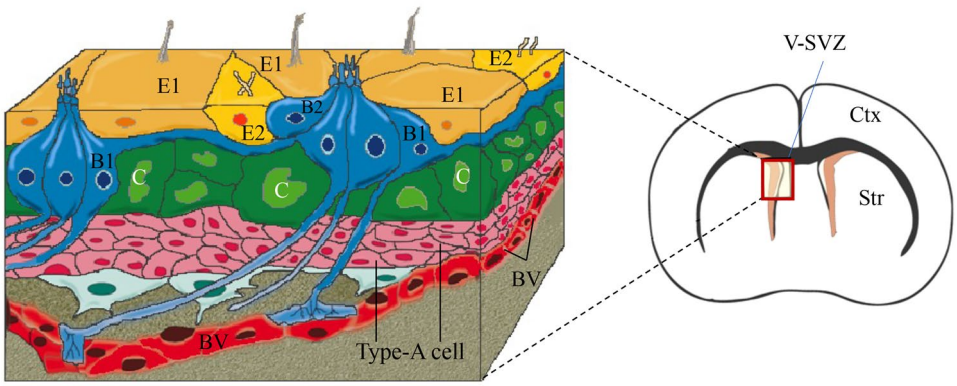

Fig. 1 Three-dimensional representation of the ventricular-subventricular zone (V-SVZ). This neurogenic region contains two types of ependymal cells or type-E cells (E1 and E2) that form the first layer of this region. Note the difference between the cilia of both type-E cells. Beneath the ependymal layer, clusters of type-B1 and -B2 astrocytes (blue) are distributed along the ventricular wall. Type-B1 cells are neural stem cells and can be identified by their radial-glia-like processes that contact blood vessels (BV). Type-B1 cells generate transit-amplifying cells referred to as type-C cells (green). Type-C cells, in turn, give rise to migrating neuroblasts (type-A cells—pink) that will reach the olfactory bulb to differentiate in mature interneurons. Blood vessel (BV); cortex (Ctx); striatum (Str)

Type-C cells give rise to migrating neuroblasts, also known as type-A cells, which are identified with migrating cell markers such as drebrin, doublecortin, PCA-NCAM, β-tubulin, and others (Sonego et al. 2015). The rodent V-SVZ neuroblasts migrate tangentially via the rostral migratory stream (RMS) until reaching the olfactory bulb, where they migrate radially and differentiate in olfactory interneurons (Doetsch and Alvarez-Buylla 1996; Bressan and Saghatelyan 2021). Most of the V-SVZ neuroblasts differentiate into glomerular interneurons (~95%) and the rest of these new neurons are incorporated into the periglomerular region. In both subregions of the olfactory bulb, V-SVZ-derived interneurons produce gamma-aminobutyric acid (GABA) (Lois and Alvarez-Buylla 1994). However, in the periglomerular region, a small percentage of these new interneurons (~3%) release dopamine (Höglinger et al. 2014), and another subpopulation appears to be able to differentiate into glutamatergic subtypes (less than 2%) (Brill et al. 2009). These novel interneurons seem to participate in olfactory discrimination, learning, and the perception of new olfactory memories. In humans, the RMS is only observed during fetal development and the early stages of postnatal life (Sanai et al. 2004; Guerrero-Cázares et al. 2011; Huang et al. 2020). Nevertheless, the differentiation pattern of these neuronal precursors may represent a promising tool for manipulating endogenous cells that can be used for cell-based therapies.

The subgranular zone (SGZ) of the adult hippocampus

The hippocampus is involved in the acquisition of episodic and declarative memories. The hippocampal formation has several subregions: CA1, CA2, CA3, hilus, subiculum, and dentate gyrus (DG). In the DG, there is a thin layer of cells referred to as the SGZ that is located between the granule cell layer and the hilus. The SGZ is a neurogenic region that comprises a niche of primary cells, immature precursors, and a permissive microenvironment, which help generate new neurons in rodents (Altman 1962; Obernier and Alvarez-Buylla 2019), shrews (Gould et al. 1997), macaques (Kornack and Rakic 1999) and humans (Eriksson et al. 1998; Kominami et al. 2023). Around 250,000 cells are incorporated into the rat dentate gyrus per month (Cameron and McKay 2001). However, these authors state that not all these cells survive for long periods; thus, under naturalistic conditions, the number of new neurons that remain in the DG after a month might be around 138,000 (6% of its total volume).

The neural stem cells of the SGZ region maintain self-renewal characteristics, and under in vitro conditions, they can differentiate into neurons, astrocytes, and oligodendrocytes (Palmer et al. 1997; Seri et al. 2004). These multipotential cells are known as type-1 hippocampal astrocytes (Gonçalves et al. 2016) or type-B cells (Seri et al. 2004), which divide and give rise to local migrating neuroblasts also called type-2 cells (Fig. 2). Type-2 cells display some morphological characteristics and molecular markers during their differentiation process, which help categorize them as type-2a and type-2b (Gonçalves et al. 2016). Type-2b cells continue their fate specification process, leading to type-3 neuroblasts that differentiate into granule neurons (type-G cells) (Seri et al. 2004; Gonçalves et al. 2016). During this stage, type-3 cells move a small distance within DG layers under the influence of stromal cell factor 1 (SDF-1) (Catavero et al. 2018) and project their axons to the CA3 region to establish dendritic synapses with the entorhinal cortex (Hastings and Gould 1999). Most of these newborn neurons are glutamatergic, and only a small subpopulation is GABAergic (Abrous et al. 2005). Some of the molecules involved in the neurogenic process of the adult hippocampus include brain-derived growth factor (BDNF), vascular growth factor (VEGF), *N*-methyl-D-aspartate (NMDA) receptor, glutamate, GABA, and serotonin, among others (Liu et al. 2003; Aimone et al. 2014; Gonçalves et al. 2016).

Hippocampal neurogenesis is regulated by multiple components such as stress, sleep problems, exercise, inflammation, and tactile deprivation (Gonzalez-Perez et al. 2018; Ibarra-Castañeda et al. 2022). Hence, this region has been primarily related to spatial learning, spatial mapping, memory encoding, and navigational skills. However, some authors have proposed that hippocampal neurogenesis plays a role as a regulator of emotional processes and may be involved in the pathological process of depression (Toda et al. 2019).

Two main hypotheses have been generated about the function of hippocampal neurogenesis. One of them suggests that new neurons play an important role in the encoding, storage, and recall of new memories. Hence, the process favors perhaps through synaptogenesis, either by these new connections reinforcing the functional integration of existing neurons or by forming new connections (Zhao et al. 2008). The second theory indicates that neurogenesis modulates emotional aspects because the hippocampus is one of the structures most affected in affective disorders, such as depression (Denoth-Lippuner and Jessberger 2021), and this brain region has significant connections with other regions related to emotional control, such as the amygdala and nucleus accumbens (O'Donnell and Grace 1995). However, neurogenesis cannot be related solely to mood control because the decrease in hippocampal neurogenesis by itself did not cause depressive-like behavior (Samuels and Hen 2011). Thus, the functional relevance of newborn hippocampal neurons has been implicated in many processes, such as resilience, stress remission, pattern separation, memory formation, and learning.

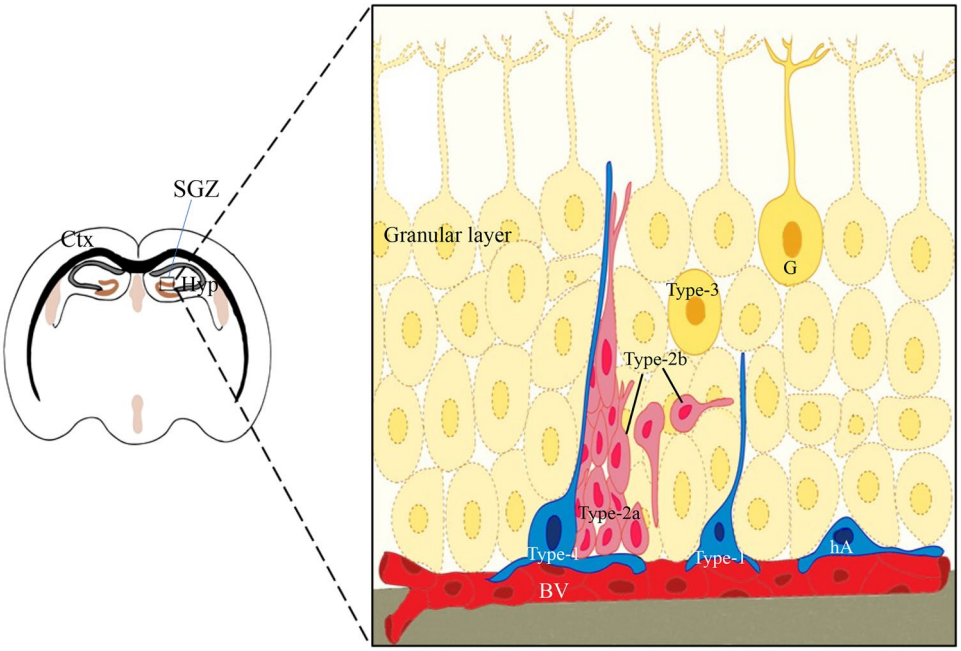

Fig. 2 Schematic representation of the cytoarchitecture of the neurogenic region SGZ. The region comprises multipotential astrocytes or type1 cells also referred to as type-B (blue) that, in turn, can be classified into two subtypes Type-1 (type-B1 cells) and horizontal astrocytes (hA). Type-1 cells express radial-glia-cell and astrocyte markers, whereas horizontal astrocytes do not exhibit radial-glia-cell markers. Radial astrocytes are the neural stem cells that give rise to type-2 cells. As type-2 cells mature, they can be classified into two subtypes according to their morphological differences and neuronal markers: type-2a and type-2b. Type-2b cells continue their fate specification process and give rise to type-3 cells that, in turn, differentiate into functional granular neurons (G cells) that establish synaptic connections with the CA3 region and entorhinal cortex. Blood vessel (BV); cortex (Ctx); hippocampus (Hyp)

The subcallosal zone (SCZ)

The SCZ is the germinal layer most recently discovered. In vitro, SCZ progenitor cells can generate the three main neural lineages: astrocytes, oligodendrocytes, and neurons (Seri et al. 2006). However, in vivo, this region only seems to produce glial cells (astrocytes and oligodendrocytes) (Seri et al. 2006). The SCZ is located on the borderline between the corpus callosum and the dorsal hippocampus. This region is generated during neural development because of the wall collapse of the embryonic ventricular zone. Although this region may be considered a dorsomedial and caudal extension of the V-SVZ, the SCZ is not associated with the ventricular system and has no connectivity with the SGZ or lateral ventricles of the ventral hippocampus (Fig. 3). Instead, this region consists of small islets or cavities that contain cerebrospinal fluid, and its cellular organization differs slightly from those described for the V-SVZ and SGZ (Fig. 3). Ultrastructural analysis by electronic microscope indicates that the SCZ contains type-E, type-B, type-C, and type-A cells. Type-E cells of the SCZ have a 9 + 2 arrangement of microtubules, although unlike those located in the V-SVZ, these are frequently found contacting both myelinated and unmyelinated axons of the corpus callosum and hippocampus (Seri et al. 2006).

In vivo, type-B cells generate type-C cells that, in turn, give rise to type-A cells that express PSA-NCAM but, unlike the type-A cells of the V-SVZ, these cells do not form chains to migrate and give rise to glia and oligodendrocytes that are incorporated into the neighboring white matter (Seri et al. 2006). However, in rodents that do not express the pro-apoptotic Bax protein, the SCZ appears to be able to generate two types of cells that express NeuN, a mature neuron marker (Kim and Sun 2013). Interestingly, these NeuN-positive cells derive from a precursor cell that expresses the zinc-binding transcription factor sp8 (Kim and Sun 2013). Although the molecular mechanisms that regulate the SCZ progenitor cells are not well known, some transcription factors have been highly expressed in this region, such as HOPX, NR2F2, ZIC2, and ZIC5 (Kim et al. 2017). In summary, under physiological conditions, the SCZ is responsible for giving rise to oligodendrocytes that populate the corpus callosum, and their function has been related to myelin renewal and remyelination processes in vivo (Seri et al. 2006; Kim et al. 2016). Hence, these properties make the SCZ a region with potential in regenerative medicine to treat demyelinating diseases.

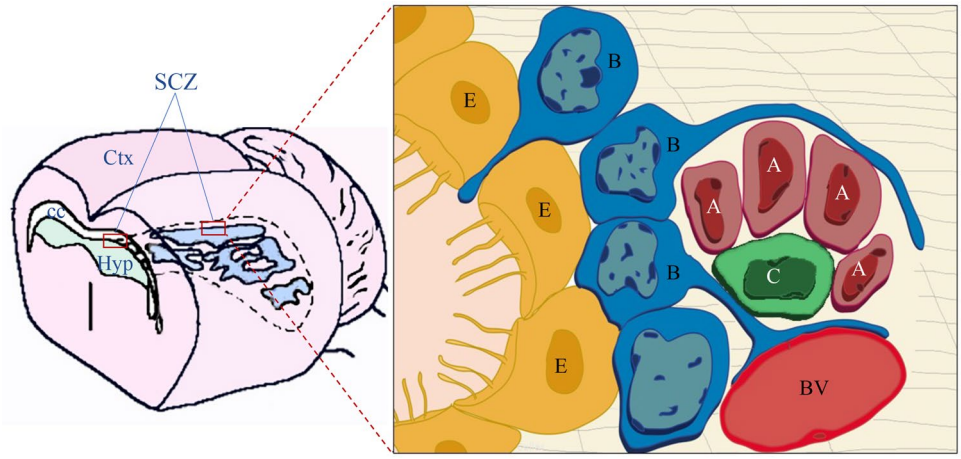

Fig. 3 Schematic representation of the cytoarchitecture of the neurogenic region SCZ. This region contains type-E, type-B, type-C, and type-A cells. Cellular composition is somehow similar to the SGZ and V-SVZ, although anatomically is not associated with them. This region comprises multipotential astrocytes (type-B or type-I cells—blue) which generate type-C cells (green) that, in turn, give rise to type-A cells (red). Ciliated cells (type-E cells—yellow) enclose cavities filled with cerebrospinal fluid. Type-A cells express markers of migrating oligodendrocytes that, upon differentiation, help preserve the population of mature oligodendrocytes and myelin sheaths. Blood vessel (BV); cortex (Ctx); hippocampus (Hyp)

Perspectives in regenerative medicine

The main biological function of the three neuron-gliogenic niches (the subventricular, subgranular, and subcallosal zones) is to preserve the cellular homeostasis of neural tissue and, depending on the demands of the brain, these regions can generate new neurons and glial cells that help repair the cerebral parenchyma. Both adult neurogenesis and oligodendrogenesis have an exquisite mechanism to control the born of new cells and their incorporation into functional circuits. However, the role of these neural progenitors is one of the most intriguing questions in neurobiology, but the evidence suggests that these newborn cells are required for preserving neural plasticity.

Experimental evidence in rodents indicates that V-SVZ neural progenitors may be involved in the pathogenesis of Parkinson's disease (PD) and Huntington's disease (HD). In the V-SVZ of patients with PD, a significant reduction of proliferating precursor cells has been found in this region (Höglinger et al. 2004; O'Keeffe et al. 2009). Transgenic animal models of PD (a-syn, parkin, leucine-rich repeat kinase 2, DJ-1, and PINK1) revealed impairments of proliferative activity and survival of newly generated neurons. In patients with HD, neuroblast-like cells were observed near the caudate nucleus (Curtis et al. 2005). This phenomenon of neuroblasts migrating toward the striatum was also reported in transgenic HD mice as a compensatory response against striatal neurodegeneration (Phillips et al. 2005; Kohl et al. 2010). For this reason, some authors propose that the V-SVZ progenitors can be redirected to the basal ganglia via BDNF or noggin overexpression to increase the production of new neurons in the ventricular wall and promote striatal plasticity and motor improvement (Winner and Winkler 2015).

Hippocampal neurogenesis appears to have a role in psychiatric disorders, including anxiety, addiction, depression, and schizophrenia. Depressive disorders have been related to impaired hippocampal neurogenesis because antidepressants affect the level of SGZ neurogenesis (Miller and Hen 2015). Inherited schizophrenia is associated with a mutation in the DISC1 gene; strikingly, experimental ablation of DISC1 in mice reduces hippocampal neurogenesis, alters granule cell positioning, and impairs hippocampus-dependent behavior in rodents (Duan et al. 2007; Kvajo et al. 2008). On the other hand, temporal lobe epilepsy has been associated with an increase in neuronal excitability and aberrant neurogenesis in the dentate gyrus, probably because seizure activity results in aberrant migration and connectivity of newborn cells (Parent et al. 1997). Nevertheless, more research is needed to know how hippocampal neurogenesis can be regulated, and how cell turnover changes throughout development.

Brain ischemia and hypoxia may represent additional therapeutic targets for the use of neural progenitors. Neuroglobin is a hypoxia-inducible, neuroprotective protein related to hemoglobin. This protein is concentrated in the mitochondria-containing areas of neurons and neural stem cells, and its distribution correlates with the oxygen consumption rates of neural cells (Burmester et al. 2007). A reduction in mitochondria and neuroglobin has been described in the aging brain (Sun et al. 2001), which may increase the vulnerability to hypoxia and neural degeneration observed in the elderly. Neuroglobin seems to have a role

in neurodevelopment and may promote neuronal survival under hypoxic conditions (Sun et al. 2001; Hümmler et al. 2012). Interestingly, this protein is expressed early during neuronal differentiation of human embryonic stem cells and in migrating neuroblasts derived from the V-SVZ of adult rats (Haines et al. 2013), but its role in the regenerative process remains to be elucidated.

The SCZ is genetically different from the other neurogenic niches (Kim et al. 2017), which may explain why this region is primarily involved in the production of oligodendrocyte precursors that help preserve oligodendrocyte renewal and myelination in the corpus callosum (Morrison et al. 2020). A recent report suggests this region is regulated by the Mycn gene, an oncogene amplified in brain tumors (Chen and Guan 2022), which may have important implications for tumorigenesis or as a therapeutic target against brain tumors.

In summary, possible treatment with exogenous cell transplants in a damaged or deteriorated brain would represent a significant advance to improve the quality of life in people suffering from traumatic brain injuries, ischemia, neurological pathologies, mood disorders, or degenerative diseases. Yet, the manipulation of the environment of these niches may also cause some potential problems, including the conversion of these multipotent progenitors into malignant cells, benign hyperplasia, or non-functional cells, which is a challenge to be solved before neurogenic progenitors can be used for clinical purposes. Thus, the best way to promote a healthy brain is based on preventive actions while we keep looking to the horizon until we get better treatments.

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Declarations

Conflict of interest The authors declare that they have no competing interests.

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Consent for publication Not applicable.

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