



## EDITORIAL

## Stem cells in the horizon of the treatment of the neonatal arterial ischemic infarction



### Las células madre en el horizonte del tratamiento del infarto arterial cerebral del neonato

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Thanks to preclinical studies, we know that stem cells migrate selectively to injured areas, where they can stimulate endogenous repair mechanisms through the release of factors with anti-inflammatory, immunomodulating, neurotropic, antiapoptotic and neurotrophic effects (paracrine signalling). Due to this neuroprotective and regenerative properties, evinced in animal models of ischaemic brain injury<sup>1</sup>, stem cell therapy is attracting interest as a novel treatment option for neonatal patients with severe neurologic disease: hypoxic-ischaemic encephalopathy, neonatal arterial ischaemic stroke (AIS), white matter injury, etc.

The first study demonstrating the feasibility and safety of treatment with mesenchymal stem cells (MSCs) in neonates with AIS with a single intranasal dose ( $50 \times 10^6$  cells) was published recently<sup>2</sup>. This open label study included all neonates with AIS admitted to intensive care units in the Netherlands, with a mean age of 6 days at the time of administration of MSC-based therapy.

To understand the relevance of this study, it is necessary to place it in the context of our current knowledge

and health care practices. Both health care professionals and health-literate adults are aware that arterial ischaemic stroke (or stroke, for short) is a major form of brain injury that is frequent after age 65 years. However, it is less known that it is also relatively frequent in neonates, before 28 days post birth, in more than 90% of cases involving the region of the middle cerebral artery. Neonates are the paediatric subgroup with the highest incidence of AIS, estimated at 1 case per 2500–5000 births<sup>3</sup>, which approximates the incidence observed in adults and is 16 times greater than the overall incidence in the paediatric population. The magnitude of the problem is exacerbated by the burden it places on the health care system, as a high percentage of children with a history of AIS experience long-term disability (AIS is the leading cause of hemiplegia in the paediatric age group) and need rehabilitation in multiple areas of neurodevelopment. Thus, by age 7 years, 50% of these children have language impairments, 30% hemiplegia or monoplegia, 30% poor academic achievement, 10% epilepsy and 8% intellectual disability<sup>4</sup>. The outcomes of neonatal AIS are heterogeneous, depending on the involved branches of the medial cerebral artery, lesion volume and the affected structures, with poorer outcomes the larger the involvement.

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Contrary to adults, in whom thrombolytic therapy and endovascular thrombectomy are established treatments, no treatment is available for neonates to prevent or ameliorate AIS, and therefore, it is not possible to reduce the neurologic sequelae of this cerebrovascular disease in infants. Thus, the clinical management of neonatal AIS is limited to supportive care and treatment of seizures. Given the absence of effective treatment, there is an urgent need for the development of safe and effective therapeutic interventions able to improve the outcomes of this potentially devastating neurologic disease in the neonatal period.

A study by Baak et al.<sup>1</sup> showed that it is possible to diagnose, transfer and treat patients with perinatal AIS within 7 days of onset, and that it is possible to administer the dose of MSCs intranasally within a maximum window of 4 h after its preparation, and that this intervention is safe and well tolerated. The authors did not observe any severe adverse events in any patients, nor found any differences in serum markers of inflammation (C-reactive protein, procalcitonin or the white blood cell count) before and after the administration of MSCs.

Although other studies have explored the feasibility and safety of stem cell therapy in neonatal neurologic disease (hypoxic-ischaemic encephalopathy)<sup>5,6</sup> and respiratory disease (preterm infants with bronchopulmonary dysplasia)<sup>7</sup>, this study found that it is possible to concentrate the care of patients with the main form of neonatal stroke in experienced facilities and to overcome the logistic challenges involved in the preparation and administration of MSCs. The researchers used MSCs as opposed to autologous cells from umbilical cord blood or Wharton's jelly, the most common approach in neonates due to its immediate availability and low immunogenicity, but certainly a strategy that entails significant logistic difficulties (harvesting, processing, storage in biobanks and dosage)<sup>5</sup>. The intranasal route of administration allows MSCs to enter the brain through the olfactory foramina across the cribiform plate and has proven effective in preclinical models<sup>8</sup>. However, important aspects have yet to be established: the cell dose, number of doses and timing of administration. One potential future alternative to MSCs could be the administration of exosomes, the mediators of the beneficial effects derived from MSCs, which would reduce the logistic challenges and the risks, small as they are, of tumorigenesis and immunocompatibility problems inherent to MSCs<sup>9</sup>.

Although there is still a long way to go before this therapeutic intervention can be integrated in the management of neonatal AIS, to avoid an excessive delay in proving the efficacy of therapeutic interventions for major neurologic conditions, we believe that proof of concept studies could be an alternative for the time being until conventional clinical trials can be carried out. These studies require a tenth of the usual number of participants and it do not take years to yield results, as they use endpoints such as neuroimaging markers (multimodal magnetic resonance imaging and magnetic resonance spectroscopy) or biochemical markers.

If MSCs prove effective, NAIS would stop being an untreatable disease and become one of the diagnostic and therapeutic emergencies in neonatal neurology, as occurred with hypoxic-ischaemic encephalopathy in the past. At such time, it will be necessary to develop rapid and well-structured operational protocols to ensure neonates with AIS access to stem cell therapy, that is, to establish a neonatal code stroke like the one implemented in adults presenting with AIS.

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