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Biotherapies in neurological diseases

Regenerative medicine in Huntington's disease: Current status on fetal grafts and prospects for the use of pluripotent stem cell

Médecine régénérative et maladie de Huntington : un point sur l'utilisation des cellules fœtales et des cellules souches

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ABSTRACT

Huntington's disease is currently incurable, but cell therapy is seen as a promising alternative treatment. We analyze the safety and efficacy of the intrastriatal transplantation of human fetal neuroblasts from ganglionic eminences in patients with Huntington's disease. A few rare surgical incidents were reported, but the main difficulty associated with this therapeutic approach is the occurrence of recipient alloimmunization against the graft and the lack of availability, standardization and quality control for the fetus-derived products required for cell therapy. Some patients showed sustained cognitive improvement over periods of more than six years, and motor improvements for more than four years. Grafting outcomes are variable even within individual transplantation centers. The reasons for this variability are poorly understood, highlighting the need for further research in this specific area. With the perspective of additional trials in the future, we review here the development of human pluripotent stem cell-derived cell therapy products for HD, and their advantages and disadvantages with respect to fetal cells.

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RÉSUMÉ

La maladie de Huntington est une maladie grave incurable pour laquelle la thérapie cellulaire est une alternative thérapeutique prometteuse. Nous analysons ici, sous l'angle de la sécurité et de l'efficacité, les résultats des études réalisées chez les patients utilisant la greffe de neurones fœtaux humains. Outre les rares incidents chirurgicaux, le principal problème rencontré par la technique est celui de l'existence d'une allo-immunisation de l'hôte contre la greffe et du manque de disponibilité de cellules fœtales. Certains patients montrent une amélioration durable au-delà de 6 ans sur le plan cognitif et d'environ 4 ans voire plus sur le plan moteur. La variabilité des résultats y compris au sein d'un même centre impose de poursuivre la recherche fondamentale dans ce domaine. Dans la perspective de futurs essais, le développement des cellules souches pluripotentes et leurs avantages par rapport aux cellules fœtales sont décrits dans cette revue.

1. The rationale for cell replacement therapy for Huntington's disease

Huntington's disease (HD) is a rare inherited neurodegenerative disease. It is caused by a CAG repeat expansion in the huntingtin (HTT) gene on chromosome 4 encoding the polyglutamine huntingtin. If 40 or more repeats are detected in this gene, then penetrance is complete and the diagnosis unequivocal. The disease manifests as cognitive, motor, and behavioral symptoms, the relative contributions of these types of symptoms varying between patients, and gradually progresses to dementia, and finally death, within 15 to 20 years of the onset of symptoms. There is no cure, although some treatments can alleviate symptoms. The pathogenesis of the disease is not fully understood. Nevertheless, given its severity and the accuracy of genetic testing, making it possible to diagnose HD with confidence, many treatments for slowing disease progression are currently being tested, each based on a specific hypothesis about pathogenesis [1]. None of these treatments has yet proved effective and searches for alternative treatment strategies for this disease therefore remain essential. Cell transplantation is a possible approach of considerable interest, because transplantation can be successful without a need to determine the precise cause of neuronal death. Furthermore, unlike neuroprotection, it has the potential to restore functions that have been lost in symptomatic patients, making it possible to envisage the combination of neuroprotection and neurorestoration in individual patients in the future.

Among neurodegenerative disorders, HD is one of the best candidates for treatment by cell transplantation (see [2–4]). Indeed, the anatomy and distribution of neuronal cell loss in the brain of HD patients is well characterized and focal. The primary atrophy of the neural medium spiny neurons (MSNs) is localized to a fairly restricted area in the striatum at early stages of the disease. Furthermore, by contrast to Parkinson's disease, transplantation approaches aim to reconstruct the host brain circuitries involving the striatum. Cells are transplanted directly into the striatum in HD, and homotopical replacement in the usual position within the striatum increases the chances of restoring the normal anatomical circuitry and, thus, of recovery. Furthermore, the transplantation procedure for HD has solid foundations in research on animal models shown to reproduce the human disease appropriately [5] and in which grafts have been shown to integrate into the brain. Transplanted cells differentiate into all normal populations of striatal cells, including DARPP32+ (dopamine- and cyclic AMP-regulated phosphoprotein+) medium spiny projection neurons [6]. In addition, graft-derived striatal neurons establish synaptic connections with the correct targets in the host brain, as orphan axonal terminals of the host brain in rat [7] target these graft-derived neurons appropriately. Grafts are innervated by host cortical and midbrain afferents, leading to the efferent innervation of pallidal and nigral targets [8].

Several open-label studies of the transplantation of human fetal cells into the striatum of patients with HD have been conducted since the 1990s. Among those, six open-labeled studies with a follow-up from 1 year to 10 years (summarized in Table 1) have provided exploitable data in a total of 27 patients: the "California study" [9–11], the "French study" [12–16], the "NEST-UK study" [17,18], the "Florida-Canada study" [19–23], the "Cambridge study" [24], and the "Italian study" [25,26]. Safety concerns are shared by most studies (with few exceptions) whereas efficacy differed largely between studies. Our own work in this domain was groundbreaking, as it included the first demonstration of promising results in three of the five patients in a long-term cell transplantation study using human fetal cells [12,27]. However, the efficacy of transplantation in larger cohorts of patients and the place of this approach in the future therapeutic arsenal for HD remain unresolved. Whereas stem cell research is progressing rapidly, we need to build on the experience acquired in previous and current trials using fetal cells in HD patients before running stem cell transplantation trials in patients.

2. Potential risks of fetal cell transplantation in HD patients

The neural cell transplantation guidelines issued in both Europe, by the NEST (the European Network for Striatal Transplantation) and the Network of European CNS Transplantation and Restoration (NECTAR), and North America by the Huntington Study Group (HSG), provided a framework for