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Mini Review

Foetal Microchimerism and the Human Female Brain

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Abstract

During mammalian pregnancy the mother and foetus exchange cells and DNA in a process known as microchimerism. Foetal cells enter maternal organs, including crossing the blood-brain barrier into the brain and persist over a lifetime. There is evidence that these foetal cells in the female brain can undergo molecular and morphological maturation affecting brain neurogenesis, neuroplasticity and cerebral immunosurveillance. Furthermore, foetal male DNA appears to have some protective effect on the incidence of Alzheimer's disease in women

Keywords: Matrescence, Microchimerism, Neuroplasticity, Y chromosome, Alzheimer's disease

Matrescence

The term "matrescence" was first coined by anthropologist Dana Raphael in the 1970's. It is defined by the Cambridge Dictionary as the process of becoming a mother with the physical, psychological, hormonal and emotional changes that occur after birth of a child.

There is an obvious post birth neurobiological synchronization between a mother and her newly born baby. The oxytocin released with breast feeding fosters a unique experience of intense aligned emotion and preoccupation of mother and newborn. This hormone acts on neuroanatomical centers in the brain [1] to lower stress and increase resilience in breast feeding mothers [2].

The impact of motherhood on cognition and brain function is not well characterised but clearly there are profound hormonal and neurobiological changes. These intricate hormonal changes triggered by pregnancy nurture neuroplasticity in the maternal brain to allow infant cue sensitivities. Animal studies of mammalian mothers indicate better problem solving, better memory with less stress or fear response and increased resilience when compared with their peers [2].

Microchimerism

The phenomenon of microchimerism (named after the fire breathing Chimera of Greek mythology) describes the bidirectional exchange of cells and genetic material between foetus and mother during mammalian pregnancy [3,4]. Maternal cells circulating in the developing foetus may play an essential role in educating the foetal immune system [5].

Prenatal blood taken early in pregnancy can detect the sex of the foetus as well as chromosomal abnormalities [6]. After birth the maternal immune system clears foetal cells [7] but some cells become firmly established in the mother's organs including the brain [8]. This transfer of nucleated cells and plasma DNA appears to take place in all maternal organs and can persist long after parturition, probably for a lifetime [9,10].

The permanence of foetal microchimerism in the maternal body and brain for several decades after delivery suggests it may play an essential role in maternal pathophysiology, perhaps with an ability to differentiate and functionally integrate into maternal tissue [11,12].

Changes in the Brain

Unique brain plasticity occurs during transition to motherhood [13]. Some have suggested that the hormonal changes occurring during pregnancy that influence neurogenesis may make the brain more receptive to foetal cells during microchimerism [14,15].

Tan demonstrated in 2005 that foetal cells can enter the maternal blood during pregnancy and cross the blood-brain barrier to enter the brain [16] and foetal DNA is found in cerebrospinal fluid of women during the peripartum period [17]. However, whether this includes foetal stem cells entering the brain is yet to be shown in humans [18] but has been shown in animal studies [19].

Pregnancy stimulated neurogenesis in the adult female forebrain of mice is mediated by the hormone prolactin where the production of neuronal progenitors is stimulated in the sub-ventricular zone [14]. Adult neurogenesis in mammals occurs mainly in two brain regions, the hippocampus (specifically the sub-granular zone of the dentate gyrus) and the olfactory bulb [20,15]. The prolactin induced progenitors of pregnancy migrate to produce new olfactory interneurons important for maternal behaviour as olfactory discrimination is critical for recognition of offspring [14].

Gavin Dawes group in 2005 worked with female transgenic "green" mice and used Polymerase Chain Reactions (PCR) for genomic DNA identification. They found that four weeks after birth the immunocytochemical markers for neuron, astrocyte and oligodendrocyte cell types were present, particularly when more male foetal cells were present [16].

In 2010 Zeng showed that pregnancy associated progenitors in a murine model of foetal microchimerism can integrate and persist in several areas of the maternal brain post-partum [21]. They can undergo molecular and morphological maturation similar to that seen during adult neurogenesis [22]. These cells have been observed to resemble perivascular macrophages, astrocytes and oligodendrocytes both morphologically and phenotypically [21].

Another unique issue relating to foetal microchimerism and the maternal brain requiring further investigation is a reported association between parity and a decreased risk of malignant brain tumours [23,24]. These studies suggest that microchimerism could contribute immunosurveillance against tumorigenic cells [25,26].

Microchimerism and Alzheimer's Disease

Alzheimer's disease has been reported as more common in women in the population as well as more prevalent with increasing numbers of pregnancies [27] correlating with a younger age of onset of the disease [28,29].

It is clear however that the factors underlying the sex differences in Alzheimer's disease are not well understood and the following studies reviewed here [30-32] add to this view. Pike's review in 2016 emphasised that events in women that decrease a lifetime exposure to oestrogens are generally associated with increased risk of Alzheimer's disease but oestrogen-based hormone treatment near menopause may reduce this risk [30]. It is known that there is sexual developmental differentiation of the brain between men and women. There is a view that sex hormone actions during early development may cause inherent vulnerability of women to the subsequent development of Alzheimer's when older [30].

The epidemiological study of Beeri's group had somewhat contradictory findings in that some women who had three or more children were less likely to be diagnosed with Alzheimer's disease in older age [31]. The data in this study did not differentiate the gender of the children in these women. Schelbaum and colleagues looked at brain MRI biomarkers of dementia risk in midlife and their association with reproductive history. They looked at grey matter volumes in regions of the brain most affected by Alzheimer's disease, especially the precuneus, temporal and frontal regions. Results indicated that a longer reproductive span, a higher number of children (gender not specified) and the use of hormone therapy were positively associated with larger grey matter volumes which may offset neurodegeneration in advanced age [32].

The study from J Lee Nelson's group in Washington, using autopsy PCR testing, found that females with more male microchimerism in their brain had a lesser incidence of Alzheimer's disease [33]. In this post mortem study with real-time quantitative PCR testing to detect male DNA and using Y-chromosome specific DYS14 gene sequence, multiple brain regions of deceased neurologically normal women as well as those diagnosed with Alzheimer's disease were analysed. Of the 59 women tested 63% had male foetal microchimerism identified in the brain [33].

The five areas of the brain most affected in Alzheimer's disease are the amygdala, hippocampus, prefrontal cortex, temporal and parietal lobes [34]. These areas were carefully examined in the 59 females in this study confirming that the pathological changes seen in Alzheimer's disease had a 60% lower incidence of Alzheimer's disease in those women who had male microchimerism [33]. The eldest female tested was aged 94yrs indicating that foetal microchimerism can persist across a human lifespan [33-41].

Conclusion

Unique brain plasticity occurs during matrescence and genetic material entering the brain during pregnancy may have a significant long-term role in female health. Theories of cognitive aging together with a number of studies of neural and cognitive development are recognising an increase in late life cognitive reserve of matrescence in some females.

Women with male DNA in their brain as a result of foetal microchimerism seem less likely to develop Alzheimer's dementia. This may be the result of the ability of these cells to differentiate into various mature phenotypes such as neurons. There are many unknown lifelong biological consequences of the bidirectional

exchange of intact cells between a pregnant woman and her foetus. Foetal microchimerism may positively impact maternal health and potentially be of evolutionary significance.

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Conflicts of Interests

None.

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