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Mutations rarely occur in nerve cells due to their inability to proliferate and regenerate from their senescent state in.

Mutations are rare in the small pool of neuronal progenitor and precursor cells which are characterised with desirable regenerative and differentiation abilities due to their increased expression of DNA damage detector checkpoint proteins p53 and p73. Mutated nerve cells are marked for DNA damage repair or apoptosis where potential oncogenic mutations are not passed onto daughter cells and are removed from the genome. Tumorous growths which bypass these protective mechanisms are then detected by the abundance of immune cells surveilling the nervous system and within the lymphatic system which mark them for degradation. Metastasis of nerve cell tumours is reduced by the hard bony structures and presence of the

Generally, mutations which develop oncogenic transformation of cells are predominantly somatic where germline mutations account for a small proportion of nerve cell tumours. Additional risk factors have been mentioned such as ionising radiation and increasing prevalence due to increasing age and early childhood.

However, it is important to consider the disadvantageous impact of these protective mechanisms in the nervous system. The limited number of CNS and NS regenerating cells cause significant problems other than avoiding cancer. Following injury to the spinal cord, brain and peripheral nerves they are unable to equivalently regenerate to previous levels. The question remains whether the decreased number of nerve cell tumours is beneficial over the increased number of degenerative nervous system diseases which stem from the inability of nerve cells to proliferate and regenerate.

Additionally, due to these cancers being so rare in nature it has resulted in less available research in therapeutic treatment compared to more common breast cancer. It also becomes a challenge for clinicians as the symptoms presented for nervous system tumours are similarities for strokes.

Therefore, these types of neoplasms could be missed in diagnostics due to the lack of research into these types of tumours and their understandings. This contributes to the issue of cancer registries listing incidence and mortality rates of neural tumours which are unrepresentative. Less developed countries correlate with decreased rates of nerve cell tumours due to the limited availability of health care where cases go undiagnosed. Improvements are required in reporting these cases to provide representative data to conclude risk factors based on gender, ethnicities, geographic location and age.

## Limitations

As with every literature review, the associated limitations must be addressed. Research conducted into the mechanisms and adaptations underlying the rarity of nerve cell tumours is considerably limited which presented difficulties in researching and

selecting relevant journals in line with the aims established in this review. Search terms were narrowed as much as possible to increase relevancy yet, some literature may have been missed which might have provided insights into areas not discussed here despite using four search engines to conduct the review. Additionally, as there are multiple different types of cells associated with the nervous systems, numerous different types of tumours are a result.

This is created a limitation as nerve cell tumours couldn't be established by their specific rarity as there are too many to cover in this rapid review. Any of the literature surrounding tumours, nerve cells and CNS and NS are review papers. It was a challenge to original research papers rather than literature reviews on this topic. There is possible bias in this review tailored towards the CNS compared to NS. This is due to the increased number of publications surrounding the CNS whereas tumours of the NS are relatively under-researched creating a challenge to find relevant literature. Finally, classifications of CNS have changed over time according to the WHO. This has led to a large number of older publications using incorrect terminology to describe these tumours which associated confusion.

## Future Directions

Despite establishing important conclusions underlying the rarity of nerve cell tumours, many questions remain unanswered which would provide essential insight into specific tumour rarity by generating new aims. Particularly understanding the mutations involved with nerve cell tumours and therefore, potential therapeutic targeting treatment into improving the high morbidity rate associated with these tumours.

Areas for further exploration include the triggering factors stimulating DNA repair in post-mitotic neurones which have re-entered the cell-cycle. This would provide insight into the ways in which neurones can maintain their population without inducing apoptosis following DNA damage as radiation and pollutants will continue increasing leading to heightened oncogenic mutations. Additionally, research into NSCs and NCCs in their utilisation of therapeutic potential against malignancies is required as these cells are targeted and hijacked by tumours (particularly gliomas) due to their proliferating and regenerating capacities. Development of targeted immunotherapy has been shown to be a promising avenue for treatment in more common cancers e.g. breast therefore, research into biomarkers and immunoprofiling of nerve cell tumours would provide improvements in treatment following diagnosis.

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