Association of micronucleus frequency with neurodegenerative diseases

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Micronuclei (MNi) can originate either from chromosome breakage or chromosome malsegregation events and are therefore ideal biomarkers to investigate genomic instability. Studies in peripheral lymphocytes of patients with neurodegenerative diseases, mainly Alzheimer’s disease (AD) and Parkinson’s disease (PD), revealed an increased micronucleus (MN) frequency in both disorders but originating mainly from chromosome malsegregation events in AD and from chromosome breakage events in PD. Studies in other neurodegenerative diseases are largely missing, and some data in premature ageing disorders characterised by neurodegeneration and/or neurological complications, such as Ataxia telangiectasia, Werner’s syndrome, Down’s syndrome (DS) and Cockayne’s syndrome, indicate that MNi increase with ageing in cultured cells. An increased frequency of aneuploidy characterises several tissues of AD patients, as well as of individuals at increased risk to develop AD, such as mothers of DS individuals and DS subjects themselves. The use of the buccal MN cytome assay in AD and DS subjects allowed finding significant changes in the MN frequency as well as other cellular modifications reflecting reduced regenerative capacity compared to age- and gender-matched controls. These changes in buccal cytome ratios may prove useful as potential future diagnostics to identify individuals of increased risk for these disorders.

Introduction

The global incidence of common neurodegenerative disorders such as Alzheimer’s disease (AD) and Parkinson’s disease (PD) is rising worldwide, following the increasing longevity of humans, thereby leading to a significant financial burden at both the social and the government level (1). To date, no reliable, cost-effective and robust biomarkers are readily available to identify individuals of increased risk for these and other neurodegenerative disorders.

Biomarkers that may identify individuals who are at an early stage of neurodegeneration would be useful as this would allow potential timely preventative intervention prior to the severity of the disease advancing to more critical stages. There is increasing interest in the evaluation of chromosome damage markers within somatic cells of individuals affected by neurodegenerative diseases that may prove to be predictive of increased risk (2–4). Genome instability could lead to altered gene dosage and gene expression as well as contribute to the risk of accelerated cell death in neuronal tissue (5). Markers such as micronuclei (MNi), which are biomarkers of chromosome malsegregation and/or breakage, have been investigated in patients affected by one of several neurodegenerative disorders and in groups of subjects at increased risk for neurodegeneration (6–25). In this brief review, we will examine the current knowledge on the relationship between micronucleus (MN) frequency and neurodegenerative disorders as well as introduce other related but newly identified cytome biomarkers that may in the future be predictive of increased neurodegenerative risk. We will also examine the potential knowledge gaps as well as identify future directions for experimental applications.

MN frequency in peripheral lymphocytes and skin fibroblasts of AD patients

Due to the inaccessibility of brain tissue in vivo, lymphocytes and skin fibroblasts have been used effectively as surrogate peripheral tissues to investigate damage to the genome in relation to neurodegenerative disorders (26).

The cytokinesis block micronucleus cytome (CBMNcyt) assay employs cytochalasin B as an inhibitor of cytokinesis, thereby blocking cells after the first mitosis in culture. Using simple morphological criteria, measures of both DNA damage, genotoxicity and cytotoxicity can be obtained together with other biomarkers reflecting chromosome breakage, chromosome loss, chromosome rearrangement and DNA misrepair (nucleoplasmic bridges), gene amplification (nuclear buds), cell division inhibition, necrosis and apoptosis (27).

MNi originate fromacentric chromosome fragments or whole chromosomes that lag behind in anaphase and are left outside the daughter nuclei. In the CBMNcyt assay, the cells that have undergone one nuclear division are recognised because of their binucleated appearance and MNi, which are expressed in these cells, are scored as DNA damage events during the CBMNcyt assay. The formation of MNi and the presence of chromosomal aberrations are events strictly linked, since the presence of MNi in dividing cells is the result of chromosome breakage due to un repaired or misrepaired DNA lesions or chromosome malsegregation due to mitotic malfunctioning. These events may be induced by oxidative stress, exposure to clastogens or aneuploidogens, genetic defects in cell cycle checkpoint or DNA repair genes, as well as deficiencies in major co-factors in DNA metabolism and chromosome segregation machinery (28).

The first application of the MN assay to peripheral cells of neurodegenerative patients was carried out by us in 1997 (2). High levels of spontaneous micronucleated binucleated cells...
were found in cytochalasin B-blocked binucleated peripheral blood lymphocytes of AD patients. Furthermore, after application of the fluorescent in situ hybridisation (FISH) technique utilising a pancentromeric DNA probe for the detection of the presence of the centromere, we found that the majority of MNi were composed of whole chromosomes (2). Subsequently, by means of dual-colour FISH with differential labelled DNA probes, we obtained information on spontaneous chromosome loss and gain frequencies for both chromosomes 13 and 21. FISH data showed that AD lymphocytes had higher frequencies of chromosome loss as well as higher frequencies of aneuploid interphase nuclei compared to lymphocytes of healthy controls. However, aneuploidy for chromosome 21 was more frequent than for chromosome 13 in AD patients (3). This preferential occurrence of chromosome 21 malsegregation in somatic cells of AD patients raises the hypothesis that mosaicism for trisomy of chromosome 21 could underlie the dementia phenotype in AD patients, as well as in elderly Down’s syndrome (DS) patients (29). The spontaneous frequency of MNi is increased in AD lymphocytes compared with those of the control group, as well as in skin fibroblasts of AD patients with either sporadic or familial forms of the disease (6). A differential sensitivity in terms of induced cytogenetic damage was also found in cultured AD cells. To evaluate the sensitivity to aneuploidogenic agents, in vitro treatment of lymphocytes of affected individuals was performed by adding griseofulvin, a chemical compound whose supposed target are microtubule-associated proteins and aluminium (Al), a metal which is thought to increase the risk of developing AD. Analysis of sensitivity to the aneuploidogen griseofulvin showed that the patient group was characterised by lower levels of MN induction compared with controls while Al treatment did not induce an increase of MNi in AD patients (2,6).

MN frequency in buccal mucosa cells of AD patients

The buccal mucosa (BM) is a stratified squamous epithelium consisting of four distinct layers (Figure 1) (30–32) and represents an easily accessible tissue that can be used to sample cells in a minimally invasive manner and has been utilised to study the rate of division of proliferating (basal) cells, their genomic stability and their propensity for cell death (33). Figure 2 illustrates diagrammatically the various cell types, nuclear anomalies and possible interrelationships between the various cell types observed and scored in the BMNcyt assay. The use of cells from the BM provides a unique opportunity to study the regenerative capacity of epithelial tissue originally derived from the ectoderm during embryogenesis, which initially comprises brain tissue, fibroblasts and epithelial BM. The BMNcyt assay can be used to measure biomarkers of DNA damage (MNi and/or nuclear buds), cytokinesis defects (binucleated cells), proliferative potential (basal cell frequency) and/or cell death (condensed chromatin, karyorrhexis, pyknotic and karyolytic cells) (34,35). These BMNcyt biomarkers also show distinct differences between the cytome profile associated with normal ageing relative to that for premature ageing clinical outcomes such as DS and AD (Figure 3). This highlights the potential diagnostic value of the cytome approach for determining genome instability events and measuring regenerative potential in these and other neurodegenerative disorders (7).

In a recent study, it was shown that there was a significant

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**Fig. 1.** Diagrammatic representation of a cross section of normal BM of healthy individuals illustrating the different cell layers and possible spatial relationships of the various cell types.
age-related increase in the MN frequency in an older cohort (65–70 years) compared to a younger cohort (18–25 years). Similarly, other buccal cytome changes were evident in the BM of the older cohort and included an increase in karyorrhectic cells, condensed chromatin cells and basal cells being reported relative to young controls (7).

The BMNcyt approach was recently applied to a newly diagnosed Alzheimer’s cohort prior to the commencement of any treatment. It was found that there was a slight increase in MN frequency in the AD cohort but this failed to reach significance. However, frequencies of basal cells, condensed chromatin cells and karyorrhectic cells were found to be significantly lower in AD patients compared to age- and gender-matched controls (36). These changes may reflect alterations in the cellular kinetics or structural profile of the BM and may be useful as potential biomarkers in identifying individuals with a high risk of developing AD. The odds ratio of being diagnosed with AD for those individuals with a basal cell plus karyorrhectic cell frequency <41 per 1000 cells has been shown to be 140, with a specificity of 97% and a sensitivity of 82%.

Previous studies by us showed that the MN frequency is increased in lymphocytes and skin fibroblasts of AD patients (previous section). However, studies involving the BM did not show a significant difference between AD and controls for MN frequency or nuclear buds although there was a trend for an increase in AD relative to controls (36).

**MN frequency in cells from PD and other neurodegenerative pathologies**

The CBMNcyt assay and the comet assay in peripheral lymphocytes of PD patients and matched healthy controls were performed to test the hypothesis that DNA damage is
abnormally elevated in PD cases. PD patients showed higher frequencies of MNi and a significant increase in the levels of single-strand breaks and oxidised purine bases compared to the healthy controls (37,38). Data obtained by FISH analysis showed that the percentage of centromere-negative MNi was higher than that of centromere-positive MNi, arguing in favour of MNi originating following chromosome breakage events (4,39). A recent pilot study revealed that PD patients chronically treated with L-DOPA (the precursor of dopamine commonly used in PD treatment) had increased oxidative DNA damage in peripheral lymphocytes, but not increased MN frequency, with respect to healthy matched controls (40).

Several neurodegenerative diseases belong to the so-called trinucleotide repeat expansion diseases, since they are caused by abnormal trinucleotide repeat expansion in certain genes, exceeding the normal, stable threshold; among them Huntington’s disease (HD). A study performed in a mouse model of HD containing the human HD-causative gene revealed that fibroblast cultures derived from mice at 12 weeks contained a high frequency of dysmorphic cells, including cells with an aberrant nuclear morphology and a high frequency of MNi and large vacuoles. All these features were also present in fibroblasts derived from a juvenile HD patient (15).

Ataxia telangiectasia (AT), Werner’s syndrome (WS) and CS are characterised by clinical features mimicking physiological ageing at an early age and/or premature onset of pathologies that overlap with those associated with old age in humans, neurological dysfunctions and often neurodegeneration. These disorders are caused by mutations in DNA repair genes and characterised by genome instability (41).

In cells from patients suffering from premature senescence syndromes (WS, CS, AT and also DS), a striking parallelism between reduced maximal lifespan in vitro and higher incidence of formation of MNi as well as elevated levels of spontaneous chromosomal breaks were observed, suggesting a causal relationship between senescence and DNA damage (14).

AT is an autosomal recessive disease characterised by progressive neuronal degeneration, immunodeficiency, increased susceptibility to cancer and an extreme sensitivity to the effects of ionising radiation (16–22). An elevated MN frequency has been shown to be predictive of increased cancer risk and is significantly elevated in different tissue types within AT individuals compared to normal controls (16–25). This suggests that the MN cytome assay could be utilised as a potential diagnostic to identify individuals of increased risk of AT following cellular exposure to ionising radiation.

Olfactory dysfunction is near-universal, early and often severe in AD and idiopathic PD developing before any cognitive or movement disorder (42). Furthermore, recent studies also show that the sense of taste declines in AD (43). It would therefore be interesting to test in future human studies whether combination of the buccal and lymphocyte MN assays with olfaction and taste tests would further improve early diagnosis of AD and/or PD risk.

**MN frequency in cells from DS individuals**

The BMNCyt assay was applied in DS, which is a premature ageing syndrome with a high propensity to develop AD and revealed a significant increase in cells with MNi and binucleated cells with respect to age- and gender-matched controls (7). A second study confirmed these earlier findings; furthermore, the older (≥21 years) DS age group had ~2-fold more MNi than did the younger group (<21 years) (8). Similarly, other buccal cytome biomarkers were significantly different between these two cohorts and included a significant decrease in condensed chromatin cells, karyolytic cells and pyknotic cells relative to the control group (8). These changes show distinct differences between the buccal cytome profile of normal ageing relative to that for a premature ageing syndrome and highlight the potential diagnostic value of the cytome approach for measuring the profile of cells with DNA damage, cell death and identifying the proportion of cells with proliferative potential (i.e. basal cells).

Previous results from the CBMN assay and comet assay in leukocytes from 30 DS patients and 30 controls showed that DS patients had increased DNA damage as measured by the comet assay in relation to controls, whilst the frequencies of MNi and dicentric bridges were similar to those of controls (44). Studies on peripheral blood lymphocytes from 7 DS patients and 14 healthy age-matched controls revealed that the spontaneous incidence of MNi in lymphocytes from DS subjects was lower than that of control cultures. When lymphocytes were treated with mitomycin C (MMC) at the beginning of the culture period, an increase in MN formation was found in cells from both DS and control subjects but was much more pronounced in DS subjects. This effect had to be ascribed to cells from older DS subjects (37–55 years old), which showed an MMC-induced MN formation that was significantly higher than that observed in cells from younger (9–16 years old) DS subjects, suggesting that age has to be considered a major variable when studies on the genetic instability of DS subjects are performed (45).

**MN frequency in cells from mothers of DS individuals**

The major risk factor for trisomy 21 is advanced maternal age at conception. Indeed, after maternal age 35 years, the risk for a DS pregnancy increases, for several years, proportionally to increasing maternal age (46).

Schupf et al. (9,10) observed a 5-fold increased risk to develop AD in mothers of DS individuals (MDS) who were 35 years or younger when their children were born when compared to control mothers. No increased AD risk was observed in MDS who were older than 35 years at the birth of their DS children. It was proposed that some women could have a genetic susceptibility to early chromosome 21 nondisjunction either in germ line or somatic cells, resulting in increased DS (formation of disomic gametes) and AD risk (mosaicism for trisomy 21 in neurons) (10).

Our analysis of MDS younger than 35 years at conception by means of the CBMN assay coupled with FISH revealed an increased frequency of binucleated micronucleated cells (BML) and chromosome 21 malsegregation events in peripheral lymphocytes of MDS with respect to control mothers, arguing in favour of a susceptibility to chromosome 21 malsegregation in somatic cells (11). Subsequent studies by us confirmed the increased frequency of BML in MDS younger than 35 years at conception and showed a correlation between BML frequency and polymorphisms of the *MTHFR* gene (677C>T and 1298A>C), a key regulator of folate/homocysteine (Hcy) metabolism (12,13).
Molecular mechanisms to explain increased MN frequency in neurodegenerative disorders

Several mechanisms are likely to be involved in the formation of MNi in cells and tissues of individuals affected by neurodegenerative diseases, largely depending on the origin of the MN itself, i.e. from chromosome breakage or from chromosome malsegregation. Oxidative stress is one of the earliest detectable events in neurodegenerative disorders, often observable before the onset of the disease symptoms, and might be one of the triggering factors in the neurodegenerative process (47).

It is the inevitable result of an imbalance between elevated free-radical scavenging and a decrease in either free-radical scavenging or a reduction in the efficiency of antioxidant defence mechanisms, including those used to repair oxidised macromolecules. This leads inevitably to both cellular dysfunction resulting in elevated genomic instability events such as MN formation and eventual cell death (47). Increasing evidence suggests that neurodegenerative disorders such as AD, PD and HD are characterised by impairments of DNA repair pathways, particularly the DNA base excision repair pathway that specifically removes oxidised bases, contributing to genomic instability and MN formation in such disorders (for a review, see ref. 41). WS, CS and AT result from mutations in genes participating in DNA repair processes and are characterised by genome instability (41).

Another plausible mechanism of MNi formation in neurodegenerative diseases takes as a starting point folate metabolism. Several studies revealed that AD patients are deficient in folate and vitamin B12 (48). These factors are associated with increased MN formation and the alteration of methylation patterns that could modify gene expression (49,50). Folate is an essential nutrient acting as the methyl donor for the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate required for DNA synthesis and repair (48). Folate is also required for the production of S-adenosylmethionine, the methylating agent required for the maintenance of cytosine methylation patterns essential for gene expression regulation and for chromatin structure stability in critical areas such as the centromere (51). Under conditions of folate deficiency, dUMP accumulates producing DNA strand breaks as a result of base removal by glycosylases following uracil misincorporation into DNA in place of thymine leading to MN formation (52). An inevitable consequence of folate deficiency is the accumulation of Hcy, which has been associated with an increased risk for AD (53). There is also evidence of hyperhomocysteinemia in PD patients, likely caused by levodopa therapy (54). At concentrations >15 μM, Hcy is considered cytotoxic and has been correlated with the lymphocyte MN index within the normal physiological range (55,56).

Impaired folate metabolism and hyperhomocysteinemia have been suggested to be among risk factors for having a DS baby based on the assumption that they could result in aberrant methylation of pericentromeric regions as well as of regions involved in chromosome recombination, thereby affecting chromosome 21 segregation (57). Moreover, in vitro studies by some of us revealed a direct link between folate deficiency and chromosome 21 malsegregation events (58).

DS individuals usually develop AD by the fourth decade of life, likely because of constitutive trisomy 21 results in overexpression of genes mapping to chromosome 21, in particular that coding for the amyloid precursor protein (APP) (59). Additionally, MDS who had a DS child at a young age are at increased risk to develop AD (9,10). A unifying hypothesis trying to relate DS, trisomy 21 and AD was developed in 1991 by Potter (29), who proposed that trisomy 21 mosaicism at germ cell level or in brain cells could account for the familial aggregation of AD and DS (29).

The brain is a complex genetic mosaic of aneuploid and euploid cells (60). Aneuploidy in the cerebral cortex of normal brains has been estimated at ~10%, and aneuploidy in the AD brain was not found to be significantly increased. However, a dramatic 10-fold increase of chromosome 21-specific aneuploidy was detected in the AD cerebral cortex (61). Moreover, a case of young-onset AD due to occult mosaicism for trisomy 21 (10%) was reported (62), and a sporadic early-onset patient with AD had euploid cells but resulted as a somatic mosaic for a mutation in the presenilin-1 gene (PSEN1, one of the three AD-causative genes, alongside APP and PSEN2) (63). Studies in transgenic mice and transfected cells revealed that overexpression of APP or PSEN1 AD-causative mutations or the addition of the amyloid beta peptide to cultured cells lead to chromosome mis-segregation and aneuploidy, including trisomy 21, likely inducing microtubule dysfunction (64,65).

A recent hypothesis suggests that maternal nondisjunction events leading to DS could originate from meiotic divisions of trisomic premeiotic ovarian cells (66). Indeed, the authors suggested that disomy 21 in eggs could originate from altered pairing and nondisjunction of chromosome 21 during the meiosis of trisomic ovarian cells. They also suggested that women who have a DS baby at a young age could be those with a high frequency of mosaicism in premeiotic ovarian cells (66).

Moreover, it has been observed that neurons, believed until a decade ago to be in a terminally differentiated postmitotic quiescent state, can re-enter the cell division cycle (67). An interesting recent hypothesis predicted that cell cycle re-entry in AD is highly regulated by centromere cohesion dynamics (68). The sequential separation and segregation of centromeres in the metaphase–anaphase transition is genetically controlled and it has been shown that this sequence of temporal order is altered in AD, i.e. centromeres divide prematurely. This aberrant division is called premature chromosome separation and is seen as a manifestation of genome instability; it has been found in ageing, in other chromosome instability syndromes and in vitro following certain chemical treatments, as well as in AD (69,70). At present, there is agreement about the fact that aneuploidy and enhanced neurogenesis are hallmarks of the pathology of AD (71).

Conclusions

The few studies performed so far indicate that several neurodegenerative diseases and/or premature ageing disorders with neurological impairment are characterised by an increased frequency of MNi in peripheral cells and tissues (Table I); however, the mechanisms at the basis of MNi formation could be different in different disease states. For example, studies performed in peripheral lymphocytes of PD patients suggest that MNi originate mainly from chromosome breakage events, possibly as a consequence of oxidative stress (4,37–39). In contrast, studies in cells of AD subjects argue in favour of chromosome malsegregation events as the main
mechanism leading to MN formation (2,3). Little is still known concerning other neurodegenerative diseases, since there is only information on cultured fibroblasts from a patient with juvenile HD (15), and in premature ageing disorders, MNi increase with cellular ageing, likely as a consequence of genomic instability leading to premature ageing phenotypes (14).

Interestingly, as discussed in the previous section, an increased frequency of aneuploidy has been observed in several tissues of AD subjects, including peripheral tissues and brain neurons. The buccal MN cytome assay in AD subjects provided interesting results (36). Future directions focused on these preliminary findings include the need to verify these results in larger cohorts and in other forms of dementia such as vascular dementia or HD to determine whether the observed results are specific to AD patients. It would also need to be established, through further investigation, whether those individuals who have different genetic forms of AD reflect the same buccal cytome profiles. If specificity for these buccal biomarkers could be verified for AD individuals, then further studies involving mild cognitively impaired individuals could be performed to determine whether or not these changes occur in the early stages of AD. MNi were found to be increased in BM cells of DS subjects, which are a group of subjects overexpressing APP and have a high probability to develop dementia (36,37). The buccal cytome assay could also be performed in MDS, which are a group of individuals at increased AD risk. Buccal cytome changes may eventually be used to reflect disease severity or as an individual biomarker to gauge both disease progression and the effectiveness of preventative interventions aimed at slowing down or reversing the progression of the disease.

Ultimately, prospective epidemiological studies are required to verify whether abnormally high MN frequency and related

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genome pathologies are able to predict an increased risk for common neurodegenerative diseases such as mild cognitive impairment, AD and PD.

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References


