Original Research Article

Machine learning classification of specific serologic cytokines may improve detection of recent, fall induced, sub-concussional brain changes in geriatric nondemented subjects

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Abstract: A chronic activated pro-inflammatory cytokine network ("inflamm-aging") may amplify the neurodegenerative effects of a fall induced brain trauma in geriatric subjects. Our research aimed to evaluate how a trained machine learning algorithm may predict recent antecedent falls based only on specific serologic cytokines network analysis and how the consequences of these falls can be substantiated on standard head MRIs. All 279 subjects included in our study were selected from the ADNI1 dataset and all had a mild cognitive impairment diagnostic at the ADNI1 study baseline. A "train group" was built and included 14 subjects with a history of a recent, simple, standing-level fall. These were carefully matched with 14 similar subjects without any antecedent trauma. The "test group" included 251 subjects, all without any history of recent fall. The machine learning algorithm (classic C4.5 decision tree) was trained to detect a pattern of variation in 23 clinically relevant cytokines in relation with an antecedent fall. Changes in five cytokines (matrix metalloproteinase-7, eotaxin-1, interleukin-3, interleukin-8 and matrix metal-loproteinase-9) were used for fall prediction in the "test" group. Once trained, the algorithm predicted a recent fall in 119 cases from the test group. The mean brain ventricular volume that was significantly different between fall/non-fall subgroups (41645.5±10337.2 vs 27127.3±6749.4 mm3, p=0.005) remained significant in the test group, after prediction between (41544.24±17343.4 vs 34553.5±10543.2 mm3, p=0.042). The hippocampus mean volume was also significantly different between in the test group (6297.3±1080.1 vs 6745.9±1123.7, p=0.0015). A significant brain ventricular difference was observed in the "65<y.o." subgroup (p=0.04). If confirmed by larger prospective studies, our findings may increase the precision of the neuro-cognitive assessments in geriatric subjects.

Keywords: Chronic geriatric inflammation; machine learning C4.5 classification; mild cognitive impairment; brain ventricular volumes; hippocampus volumes; recent fall; subconcussive brain trauma

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1. Introduction

Traumatic Brain Injury remains a worldwide leading cause of morbidity and mortality [1]. As the overall modern population is witnessing a fast-ageing process, there is an increased interest in geriatric TBI research [2]. The incidence of brain trauma in population aged 55 years and older is increasing while in population under 55, the same incidence is constantly decreasing [3]. Geriatric brain trauma has several characteristics. It is usually a consequence of same-level, standing fall(s) [4]. Geriatric fall(s) occur more often when the subject is unaccompanied: 35% of people 65 and over, living alone in long term care facilities or in assisted living housing, fell at least once per year. This percentage will increase to 50%-60% for the group 80 years and over [5]. Frequently after unwitnessed fall induced traumas, aged subjects will do not look for medical evaluation or support [6]. Very often, even repeated mild falls are not mentioned to family or caregivers for different reasons [7]. Pre-existing comorbid conditions and different medication taken may increase the risks of fall(s) [8]. Age-related cognitive fluctuations may also interfere with medical/family disclosure of geriatric mTBI, reducing the chances of a precise diagnostic and treatment [9].

In all age groups, brain trauma intensity is judged based on Glasgow Coma Scale (GCS). Fall induced geriatric brain trauma is ranked, most often, as mild (mTBI): GCS score close to 15, minimal or no loss of conscience and frequently no association with adjacent traumatic lesions. Even is named mild, mTBI is not at all trivial in this age group. Pre-existing, age related, pathology may aggravate the immediate and long-term mTBI prognostic and impose hospitalization [10]. Death after geriatric mTBI is not a rare event [11]. Immediate mild cognitive impairment (MCI) after geriatric mTBI is frequently reported [12]. Studies evaluating mild and moderate brain trauma in older adults re-ported a strong correlation between trauma and long-term neurobehavioral changes [13]. Two independent meta-analyses incorporating 15 studies with different designs confirmed an increased risk for development of different forms of neurocognitive dis-orders after head trauma [14] in seniors. TBI is now recognized as an environmental risk factor for serious neurodegenerative diseases such as Alzheimer or Parkinson's diseases [15]. There is strong association between MCI and falls [16].

One category of mTBI, sub-concussion (defined as brain concussion that do not meet mTBI definition criteria), did not gather the same attention as mTBI [17]. The initial description of this distinct pathophysiologic category mentioned that repeated, very mild, head traumas in young athletes or military personnel are summative in effect and, over a lifetime, are responsible for serious chronic neuro-degenerative changes. This patho-clinical picture is now known as chronic traumatic encephalopathy (CTE) [18]. It was recently reported that, in senescent brain [19], a single mTBI may induce persistent inflammation and white matter degeneration [20] that may progress to CTE over time [21].

The underlying mechanism that connects brain trauma with neuro-degeneration is still under investigation [22]. The existing relationship between TBI and the development of a secondary brain inflammatory injury is well accepted [23,24]. Brain trauma will act locally on the local blood-brain barrier structure (affecting glial, microglial and astrocyte cells) fact that will directly alter permeability [25] and will also trigger a complex net-work of

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pro and anti-inflammatory cytokines [26]. These regulatory peptides, generically named "cytokines" [27] are, under normal conditions, responsible for local developmental and repair processes: local inflammation, angiogenesis, cell growth, differentiation and death. In brain trauma, the peripheral cytokine network might be activated by various mechanisms and may amplify the evolution of the secondary brain lesion [28, 29], generating different degrees of neurodegeneration.

In seniors, the peripheral cytokine network is chronically activated by a wide range of geriatric induced conditions (hypertension, diabetes, dementia, Parkinson's disease, or osteoporosis) [30]. The increased pool of circulating cytokines, chemokines and inflammatory related factors [31] will generate a low-grade, generalized and persistent chronic inflammatory environment [32] that represents a significant risk factor for overall morbidity and mortality in aged subjects [33]. Two complementary concepts defined the chronic inflammatory status in elderlies: inflamm-aging [34] and molecular inflammation [35]. Under both concepts, a strong relationship between geriatric chronic inflammation and brain neurodegeneration was described [36,37].

Specific cytokines were strongly associated with brain trauma. An increase of IL-6 and a decrease of TNF-α plasmatic level was observed in geriatric patients after severe trauma; this ratio is now considered as a strong independent vital predictor factor [38,39]. But most geriatric head trauma is not severe. Similar changes were more difficult to validate after mTBI.

As cytokines act as a network, investigation of the whole regulatory mesh can provide valuable clinical information but is more difficult to interpret as data changes are often subtle [40]. Once trained, a machine learning algorithm may examine and rank multiple cytokines concomitantly, using a clear validated statistical methodology. The algorithm can also suggest predictions in relation with a possible association with a traumatic event [41].

The complex and dynamic brain inflammatory process associated with trauma may generate irreversible changes in geriatric brain at risk [42]. Standard MRIs can detect changes in specific areas, which are measurable. Neuro-imagistic research pointed at Hippocampus Volume Reduction (HVR) as a connecting factor between fall, geriatric mTBI and chronic cognitive impairment development [43]. Animal [44] and human studies [45] explored this relationship. Imagistic evaluating of HVR is not an easy task. Hippocampus shrinking is influenced by the normal ageing [46]. The complex architecture of hippocampus often imposes manual imagistic segmentation, a time consuming, subjective task [47]. Medial temporal lobe atrophy measurement proposed by Sheltens [48] simplified the HVR evaluation but is still seen subjective as it is using a visual analog scale for volume loss grading [49]. A simpler measurement that can be performed even in standard resolution MRIs is brain ventricular volume (BVV) enlargement evaluation [50]. This imagistic marker is not as specific as HVR mapping. It can be seen in normal ageing brain and in many psychiatric disorders, as well [51]. BVV was estimated in normally aged, nondemented subjects at 2% of total brain volume (age dependent) [52, 53]. A significant correlation between BVV enlargement and different degrees of cognitive impairment was described after repeated geriatric mTBI [54,55]. Same

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correlation between very mild but repeated head trauma and early neuro-behavioral changes was observed in senescent animal studies [56].

To date, little is known about the effects of a single, recent, sub-concussional trauma on geriatric BVV, in human subjects at risk.

Our research interest was to investigate how a trained decision tree algorithm is able to predict a possible antecedent recent fall based only on peripheral cytokines network variation and how these falls will translate into brain ventricular volumes increase in geriatric patients with an established MCI diagnostic.

2. Materials and Methods

Subjects. All data used in this study was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). ADNI recruited normal cognitive, mild cognitive impaired (MCI) and Alzheimer diseased (AD) subjects, aged 55 and over using a well-defined methodology (non-randomized, natural history, observational, longitudinal long-term study) [57].

Data generation. This study involves only subjects recruited in ADNI 1 study. All ADNI1 subjects had a complete medical history, a large proteomic serologic evaluation (Biomarkers Consortium Plasma Proteomics Project RBM multiplex data, details @ADNI website), a precise clinical and neuro-cognitive evaluation and a head MRI taken under a unitary protocol, all performed at study baseline.

349 subjects with MCI diagnostic responded to these criteria. 28 (8%) of them were included in a "train group": 14 subjects reported a recent, fall induced, sub-concussive brain trauma history (36% females, 76.25±6.36 years old, 50% ApoE+, 16.92±3.33 school years). Fall subjects were carefully matched with 14 subjects without any fall in their recent medical history (36% females, 76.24±5.85 years old, 50% ApoE+, 16.85±2.65 school years). Comorbidities and prescribed treatments were similar in both subgroups.

251 MCI subjects (72%) were included in a "test group", all without any trauma in their recent medical history (40% females, 73.9±7.6 years old, 52% ApoE+, 15.6 school years, mean brain ventricles 38225.2±17173.5 mm3, mean hippocampus volume 6542.4± 1123.9 mm3).

70 subjects (20%) were excluded as comorbidities or treatments were seriously different than the majority of cases, the MCI diagnostic was not supported by psychometric tests results or essential imagistic data were missing.

Brain ventricular volume, hippocampus volume, total brain volume and intra-cerebral volume were extracted for both selected groups, at baseline. All brain volumetric evaluations were performed on T1 1.5 Tesla MRIs using an automated measurement methodology (FreeSurfer). In this paper, the term "mild cognitive impairment" is used generically for all cognitive changes that are insufficient to meet clinical dementia di-agnostic criteria (psychometric scores for Clinical Dementia Rating Scale between 0.5-1.5 and for Mini Mental Status Exam between 24-27). ApoE+ term reflects one or both positive alleles.

From the ADNI 1 Biomarkers Consortium Plasma Proteomics Project RBM multiplex dataset, 23 clinically relevant cytokines [58, 59] were considered for each subject. CD40 antigen, C-Reactive Protein, Eotaxin-1,

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FASLG Receptor, Intercellular Adhesion Mole-cule 1, Interleukin-13, Interleukin-16, Interleukin-18, Interleukin-3, Interleukin-8, Matrix Metalloproteinase-1, Matrix Metalloproteinase-10, Matrix Metalloproteinase-2, Matrix Metalloproteinase-7, Matrix Metalloproteinase-9, Matrix Metalloproteinase-9- total, Neuronal Cell Adhesion Molecule (Nr-CAM), T-Cell-Specific Protein RANTES, Super-oxide Dismutase 1- Soluble (SOD-1), Tumor Necrosis Factor alpha, Vascular Cell Adhesion Molecule-1, Vascular Endothelial Growth Factor generated the pro-inflammatory proteomic dataset for both groups. The fall status (yes/no) was the only clinical information that was added to the cytokine dataset.

Data interpretation. A classical C4.5 decision tree algorithm (J48 on WEKA machine learning platform) was used for cytokines network analysis and fall prediction. A "decision tree" is a non-parametric, supervised training, machine learning method able to predict the value of a target variable based on simple decision rules learned from the data features. It is easy to understand from a medical standpoint and can be visualized [60].

The main assumption of our study is that peripheric cytokine network will show a degree of "inflamm-aging" in all geriatric subjects with MCI diagnostic [61] but in subjects exposed to recent fall(s), the network variation pattern will differ [62]. Minimal but consistent changes are detectable by a machine learning algorithm, after training. Sub-jects exposed to recent trauma will show early neurodegenerative changes in specific brain areas (ventricles). As these changes are objective, individual recollection of trauma events is not important.

Statistics. Results were analyzed using PSPP (GNU project, free software, 2015). Only basic descriptive statistic (mean and standard deviation) is presented here. Volumetric means differences between groups were analyzed with Student's T-test. P-value was set at $p<0.05$.

3. Results

In the training session, C4.5 (J48) machine learning algorithm generated a pruned decision tree with 5 nodes and 6 leaves. The algorithm prediction was considered accurate (0.98 ROC, 0.967 precision, one positive case was classified as false). The algorithm determined that changes of matrix metalloproteinase-7, eotaxin-1, interleukin-3, inter-leukin-8 and matrix metalloproteinase-9 can be used for fall prediction (fig1.).

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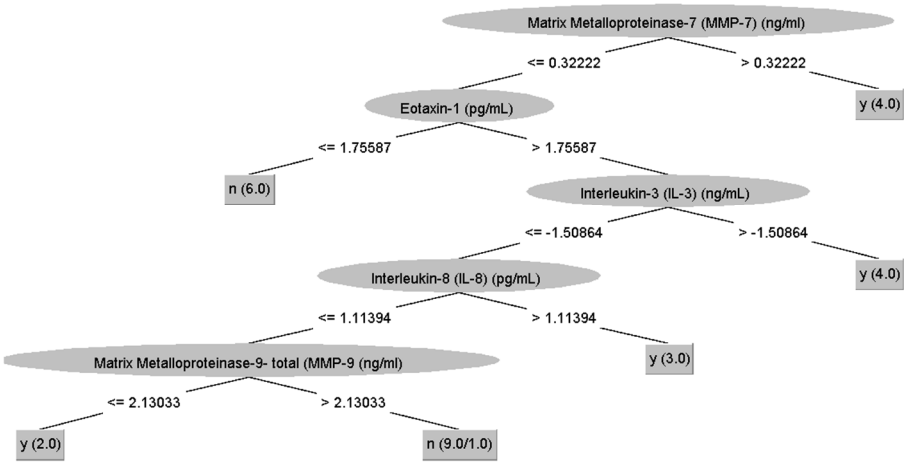

Figure 1. Decision tree structure (C4.5, J48 algorithm).

Based on this pattern, in the "test group", 119 cases received a recent fall prediction. These subjects were re-assigned and all brain volumes were analyzed (table 1, fig. 2).

Table 1. Train group and test group analysis based on machine learning classification (* p=0.0028, **p=0.0051, #p=0.0015). ICV=intracranial volume. BVV-ICV= brain ventricular volume to intra-cranial volume index. BVV-TBV= brain ventricular volume to total brain volume index. All brain volumes are in mm3. Data is presented as group mean ± standard deviation.

	Train group		Test group	
	Initial Trauma	**Initial Non-Trauma**	**Reclassified Fall+**	**Reclassified Fall-**
Number	14	14	119	132
Age	76.25±6.36	76.24±5.85	74.67±7.71	73.21±7.6
Sex	36%F	36%F	40%F	37%F
Education (years)	16.9±3.3	16.8±2.65	15.94±2.90	15.34±2.7
ApoE status	50% ApoE+	50% ApoE+	54% ApoE+	51% ApoE+
Cognitive status	100%MCI	100%MCI	100%MCI	100%MCI
Brain ventricular volume (mm^3)	41145.5± 15775.1(*)	27127.3± 6749.4(*)	41330.17± 18299.86(**)	35425. 95± 15637.62(**)
Hippocampus volume (mm^3)	6169.7.8±929.3	6188.8± 1297.3	6297.32±1080.1(#)	6745±1123.7(#)
Whole Brain volume (mm^3)	984601.3± 49222.9	979597.2± 107887.1	991795.8± 108145.6	1015581± 119469.1
ICV (mm^3)	1563087.5± 115723.9	1524191.8± 167584.5	1557762.6± 160802.7	1574325.4± 173691.4
BVV-TBV(%)	4.1± 1.5	2.7±0.7	4.21±1.91	3.5±1.61
BVV-ICV(%)	2.55±0.85	1.7±0.4	2.63±1.1	2.2±0.9

As the BVV variation is age dependent and a numerical age difference was observed between predicted fall and non-fall subgroups, an age subgroup analyze was performed and is presented in table 2 (fig 3).

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Table 2. Age subgroup analysis of BVV (*p=0.04). y.o.= years old.

Age sub-group	Predicted Fall+		Predicted Fall-	
	Number	Volume (mm^3)	Number	Volume (mm^3)
<65 y.o.	17	38052.5± 15839.2(*)	21	28748.7±12378.6(*)
65-70	14	34036.2±16914.1	29	31162.1±13155.5
70-75	29	43875.2±19923.2	29	36229.1±14725.9
75-80	25	40206.1±18029.3	22	36640.7±19023.4
80-85	23	44875.6±19159.9	22	37100.3±14169.9
85>	11	47768.9±18329.9	9	45608.4±11342.6

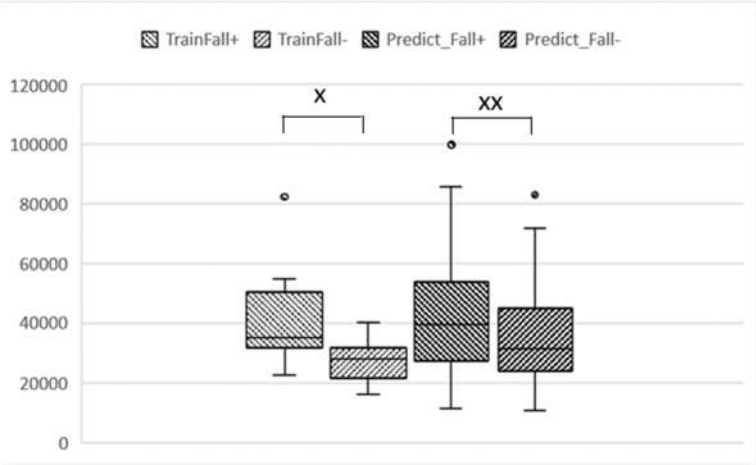

Figure 2. Mean BVV differences in "train set" and "test set" (*p=0.0051, **p=0.0063).

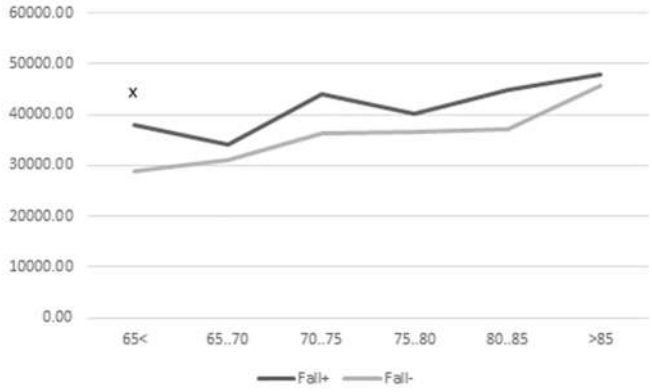

Figure 3. Mean BVV age subgroup analysis.

4. Discussion

An existing connection between same-level falls, brain trauma, neuro-degeneration and cognitive disfunction was well established in geriatric subjects. Many animal and clinical studies evaluated the neuro-degenerative effects of mild brain trauma and the as-sociated cognitive dysfunction. An increased brain ventricular and a shrinkage of hippocampus volumes were considered responsible for long term neurocognitive changes seen in aged subjects, after mTBI or sub-concussive but repetitive traumas.

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Little is known about the effects of single, sub-concussional, fall induced brain trauma on geriatric, nondemented subjects but these are the cases where falls are frequent, of-ten under-reported and not medically evaluated. Our working hypothesis is that the chronically activated pro-inflammatory cytokines environment ('inflamm-aging") may be stimulated by minimal secondary brain lesions and subsequently can amplify the post-traumatic effects of a single, recent subconcussion in subjects with MCI. As the peripheral inflammatory cytokine network variations are subtle, it is difficult to substantiate individual changes but network pattern variations are detectable by a machine learning algorithm, after training.

We used a classic decision tree algorithm (C4.5 or J48 on the machine learning platform WEKA). The algorithm was trained to detect a peripheral cytokine alteration pattern in a carefully designed "test group". It evaluated 23 clinically relevant cytokines and spotted that changes of five cytokines (matrix metalloproteinase-7, eotaxin-1, interleukin-3, in-terleukin-8 and matrix metalloproteinase-9) can be associated with a recent fall.

Once trained, the algorithm evaluated a "test group". It detected the same inflammatory pattern in 119 subjects without any declared recent trauma history (42%). Between predicted falls and non-falls subgroups, a significant difference in the main BVV was observed (41544.24±17343.4 vs 34553.5±10543.2 mm3, p=0.042). A significant volumetric difference was also detected between mean hippocampus volumes (6297.3±1080.1 vs 6745.9±1123.7, p=0.0015) but 17% of measurements were missing form analyzed data.

The only clinical variable that showed a numerical difference between the predicted fall and non-fall subgroups was age. An age subgroup analysis detected a significant BVV difference (38052.5mm3± 15839.2 mm3 vs. 28748.7 mm3±12378.6 mm3, p=0.04) in the subgroup under 65 y.o. (76% males, 40% ApoE+). The BVV-TBV index in 65< y.o. with predicted falls (3.53%±1.42%) was considerably larger than in the non-fall subjects (2.76%±1.8%). The difference in mean hippocampus volume was significant, as well (6934.8 mm3±989.5 mm3 vs 7434.3 mm3±857.6 mm3, p<0.0001). These findings may confirm the importance of a single sub-concussional event in inducing increased neuro-degeneration after falls in subjects at risk, considering that in the 65< y.o. group the associated confounding factors were minimal.

For the old-old subgroup (>85 y.o.) the absence of a significant volumetric difference is possibly related to a low number of selected cases. Most of the subjects included in the ADNI1 dataset in this age group had an advanced cognitive impairment diagnostic (Alzheimer Disease). 6 selectable subjects (23%) (mean age 86.4±0.79 y.o., 100% males, 50% ApoE+, BVV = 50000.1±14408.1 mm3, 5.1% BVV-TBV) were excluded as medical history, treatment, or MCI diagnostic were incomplete or discordant.

A central part of this study involves the use of data-mining techniques. We used a classic decision tree algorithm as it allows a training strategy using a "ground-truth" dataset and also visualization and clinical evaluation of predictive variables. 23 circulating cytokines were selected from the 149 existing in the Plasma Proteomics Project study, sampled at the baseline. Each of the selected cytokines previously showed clinical relevance in the context of mild brain trauma. The cytokine network variation predicted a fall in 42% of the tested subjects. The high number of positive predictions was

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considered "clinically credible" as similar observations were previously communicated in geriatric subjects with MCI diagnostic. MMP7 was the root node in the decision tree. It is a peripheral biomarker that quantifies the state of the blood brain barrier after mild brain trauma [63]. The level detected (30% positive cases) was in range of previously communicated data. The algorithm then used eotaxin-1 followed by IL3, IL8 for positive differentiation. MMP9 was increased in 65% of fall negative cases. Its neuroprotective role is still under debate but recent human studies mentioned a modeling effect of circulating MMP9 on blood brain barrier [64] and on hippocampal volumes [65]. Except MMP7, cytokines values used for nodes decisions were lower than it was communicated in previous clinical studies. These findings confirmed our working hypothesis: local secondary changes induced by a single subconcussive head trauma may trigger low peripheral cytokines network changes that, difficult to interpret as individual instances, will generate a pattern that is detectable by a machine learning algorithm analysis.

A well-known disadvantage of using trained decision tree algorithms is overfitting (the decision tree will perfectly fit only the sample and will not allow any generalization). We tested the decision tree on another group of 28 cognitive normal subjects without any antecedent trauma, coming from same ADNI1 dataset. Only 6 false positive case were predicted (21%). The absence of any clinical details in the prediction datasets and the blinding of imagistic measurements were strategies to avoid overfitting.

Our study has several limitations. Cytokine selection was based on published clinically relevant data [66] and not on animal data coming from studies that evaluated single mild head trauma on senescent animals. Additional restrictive criteria were necessary to reduce confounding factors mainly in old-old age groups fact that reduced the number of subjects included. Co-existing, aged induced, pathology was evaluated based on medical and medication history (12 chronic illnesses plus the history of drugs, alcohol and tobacco consumption) but precise details were not available. Both multiplex cytokine assessment and neuro-imagistic automated brain ventricular volume evaluations are methods still under research. Long term effects of neurodegeneration on the cognitive status were not evaluated as our study was cross-sectional. No precise traumatic details were available, a circumstance often encountered in everyday geriatric medical assessments. The overall consistency of data coming from an open, neuro-cognitive and imagistic database was adequate.

5. Conclusions

Our findings support the idea that even a single, same-level fall in elderly subjects at risk can generate an increased neurodegenerative process. A machine learning algorithm may predict falls based on variation of a panel of specific, activated plasma cytokines. These proteins may amplify the initial neurodegeneration in precise brain areas which can be witnessed on standard MRIs. These findings, that do not involve individual recollection of traumatic events, may increase precision of geriatric assessments. Further, larger prospective studies are needed to generate a causal assertion between falls, brain ventricular changes and cognition conversion.

Supplementary Materials: All research information is presented in the article.

Author Contributions: All three authors contributed equally in data analysis, draft writing and revision of this article. All authors approved this version for publication.

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Institutional Review Board Statement: ADNI data is open for public access. It is totally anony-mized. The de-identification process is performed by data curators. The non-identifiable data use was following the Canadian ethics research provisions for secondary data use studies (TCPs 2(2018)). The research was performed in accordance with Declaration of Helsinki principles.

Informed Consent Statement: Not applicable.

Data Availability Statement: Supporting information can be downloaded at: www.mdpi.com/xxx/Appendix.xls

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