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Basic Study

Personalized clinical managements through exploring circulating neural cells and electroencephalography

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Abstract

BACKGROUND

Since an initial diagnosis of Alzheimer disease (AD) in 1907, early detection, was unavailable through 116 years. Up-regulation of V-ets erythroblastosis virus E26 oncogene homolog 2 (ETS2) is capable to enhance neuronal susceptibility and degeneration. Protein expression (PE) of ETS2 has functional impact on AD and Down's syndrome, with diverse intensity. PE of ETS2 has an influential pathogenic impact on AD. Clinical aspects of neurological disorders directly interact with psychological maladies. However, deterioration requires an early management including programmed based protection.

AIM

To include neurogeneticscell biology; personalized/prognostics/predictive/preventive/ predisposing (5xP) platforms, accompanied by stratifying brain channels behavior pre- and post-intervention by light music in the AD-patients.

METHODS

Include exploration of PE assay and electoencephalography of brain channels. The processes are applied according to: (1) Triangle style, by application of cellular network; (2) PE assay of ETS2 in the peripheral blood of the patients with AD, by Manual single cell based analysis, and Flow-cytometry. (1) Applying the Genetic counselling and pedigree analysis; (2) Considering the psychological status of the referral cases; (3) Considering the macro-and/or micro-environmental factors; (4) Performing the required Genetics' analysis; and (5) Applying the required complementary test (s).

RESULTS

PE of ETS2 has pathogenic role in AD. PE unmasked the nature of heterogeneity/diversity/course of evolution by exploring ETS2, D1853N polymorphism in Atxaia Telangiectasia mutated gene (ATM), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and course of evolution at the single cell level of the brain. ETS2 revealed different cellular behavior in the blood and suggested the strategy as" Gene Product-Based Therapy (GPT") and the personalized managements for the patients. PE reflected weak expression of ATM, mosaic pattern of ETS2; remarkable expression of VEGF and EGF by Highlightg an early detective platform by considering circulating neural cells and the required molecular investigation, for the target individual (s) predisposed to AD or other neural disease including brain neoplasia.

CONCLUSION

We highlighted application of the Single Circulating Neural Cells (CNCs) and Correlated Ratio based between Brain channels by providing the 5xP personalized clinical management model for and early detection and therapy of the patients with AD and their targeted/predisposed relatives.

Key Words: Alzheimer; Protein expression; Brain channels, Predictive/early detection

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Core Tip: The provided outcomes emphasize on the Personalized/Classified/ Functional/Single cell based/Complementary insights, and systematic strategy in Neuro-Science. The successful bridging approach between Neuro-Science and Medicine requires: (1) The combination of the molecular and functional insights at single cell level; (2) By emphasizing on the course of evolution; and (3) To expedite towards unmasking the functional modifications in the blood stream of the patients with neurological disorders including Alzheimer disease (AD). However, exploration of the CNCs accelerate to unmask the course of evolution by providing the personalized and translatable model to the target based therapy. Let's improve the life quality of the patients with neurological disorders including AD with simply the light music which corresponds with 40 Hz in gamma sensory stimulation therapy. It is essential to differentiate between neurological- and neuro- psychiatric diseases. Surprisingly, we offer an early detection of the stem cells, including the neural CD133 at fetal period, *i.e.*, as early as 8-9 wk through the circulating fetal cells in the maternal blood stream.

INTRODUCTION

Present introduction provides the multi-directional insights towards the Alzheimer disease (AD), including the function of involved proteins (PE) at SC level; and electroencephalography (EEG), to observe the role of light music (LM) on the brain channels, and the interaction between different brain channels to provide the personalized periodic chart for the predisposed individual and/or patients affected with AD. In addition, An initial description of the histopathology of AD has been provided by Alois Alzheimer in 1907, which is categorized by brain atrophy, an extracellular, cumulated of Aβ peptide (amyloid plaques), loss of neuron and synapse, composition of

tau protein, as neurofibrillary ingredient[1]. Regulation of of the Human Presenilin-1 Gene by Ets Transcription Factors and p53 play key role in AD-pathogenesis[2]. The decisive role of DNA by controlling 90% of the expression of presenilin 1 gene located in chromosome 21 (-35 to +6) is highlighted. This region harbors an Ets transcription factor-binding motif, and a 2-base pair alteration within the sequence of (GGAA to TTAA) of the Ets territory leading to the 90% transcriptional reduction. It was also reported that Ets1/2 transcription factors activate PS1 transcription.

The pathological diagnosis in AD, and accumulation of amyloid, occur almost decades before an initial sign of clinical symptoms[3]. Besides, functional aspect of brain network could be unmasked by magnetoencephalography. Most importantly, application of the non-invasive strategy, as an early detection of the symptom (s) of neuropathology at pre- developmental period of the AD is essential.

Initially, the micro- and macro-environmental factors, including nutrition play, partly, the influential roles in initiation and progression of AD. The most challenging panel in this topic is the late diagnosis and the risky procedures through the exploration of AD and therapy. In addition, EEG is the non-invasive and trustable method to detect synaptic dysfunction and the course of the disease. However, performance of EEG is helpful, but very late.

In addition, the combined strategy to classify the EEG-data, by applying an early functional assay of the target protein (s), at single cell level, and as the personalized analytical procedures in AD is, currently, our ongoing process.

Brain function could be, routinely, examined by EEG in AD with significant resolution[4]. EEG is revealed to be: (1) Non-invasive; (2) Unmasks the alphabetic informative codes of the neural territory; (3) Recording many required targets; (4) Unmasking the health conditions related to the patients' age; and (5) Deals with the pharmacological moddling[5,6]. Actually, EEG is capable to unmask the basic prognostic mechanisms in AD. Furthermore, it is proposed that the progression in AD is supposed to be associated to the "functional disconnection"[7].

In the resting phase, the increased and decreased functional connection is indicative of activity for the prefrontal and posterior regions through the alpha band[8,9]. Besides, by considering the decreased function in EEG exploration, its consequences on the connectivity is remarkable which depends on the individuals and technology.

Regarding the genetic test, the V-ets erythroblastosis virus E26 oncogene homolog ETS2 up-regulation may lead to an increased neuronal degeneration, appoptosis and susceptibility[10]. The ETS2 gene is involved in two different group of patients, affected at totally diverse age of onset including AD and Down's syndrome (DS)[11].

The primary predisposing/predictive/early detective strategy is the pedigree-based analysis of the proband affected with nervous system/brain disorder (s) including AD. Such approach will cover the candidate relatives of the proband (s) for the screening program. This strategy will unmask: (1) The predisposing factor through the pedigree; and (2) the target and candidate relatives for an early and non-invasive screening.

Circulating- brain Cells (CNCs) offer: (1) The non-invasive screening; (2) At single cell level; and (3) Unmasking the heterogeneity/diversity and evolution.

Ethics play fundamental and supportive role in Genetics and Psychiatry. It facilitates, care and guarantee the benefit of patients in different stages including sampling, research, and clinical managements. Through such platforms, the chain of events including predisposition, prognosis, prediction, prevention (as 4xP aim), diagnosis and personalized therapy are required to be considered. In cell biology, the single cell level play the key role in unmasking the brain's behavior and have complimentary role and functional impact on the neurological system.

The 5xP strategy would be achievable through the systematic exploration with an early- detection and personalized therapeutic management. Besides, the pedigree-based analysis provides the predictive stage for the relatives of proband, affected with AD at any age.

Personalized screening, at single cell level, with adequate cell analysis, as early as possible, is scientifically trustable. Therefore, it is an urgent aim for both Scientific and Medical platforms to consider an early detection of the neural disorders.

Brain is a sophisticated and transmittable organ. The pathology of the brain is classified and available[3]. By considering Genetics and cell biology, the specific factors in the neural cells play the key role in the neural territory. As a result, the manner of current systems have the influential and functional roles on the specific neurological mechanisms at single cell level. Therefore, to unmask the alterations, it requires the most comprehensive exploration at somatic- and genomics level[11].

Brain harbors the multi-channels, which is characterized with the miscellaneous and essential proteins.

Conclusively, Neural cells are derived from the pool of homogeneous progenitor cells. Furthermore, environmental factors, affect the genetic variations and predisposing factors. Concerning the required techniques and the essential therapeutic aspects of the neurological disorders, the informative panel including the histo-pathologic, protein expression (PE) at single cell level and the molecular techniques are required.

As the routine manner, the most puzzling information achieved at the global level, which does not provide the essential Information on the diversity/heterogeneity. Furthermore, the single cell based analysis of PE, is capable to unmask the architecture of the expression and co-expression at the final cellular procedure and production.

The routine molecular based analysis are, rapidly, used in the neuroscience and diagnosis, but are not informative to unmask the heterogeneity/diversity of the functional single cell based which has key role on the occurrence of evolution.

MATERIALS AND METHODS

Ten patients, including six females and four males, affected with AD; and ten healthy individuals are participated in the present study. The lymphocytes were cultured in RPMI media (Sigma Aldrich, St Louis, MO, United States) for 35 min at 37° C. Then the cells were treated with the hypertonic solution, and were fixed. The lymphocytes were stained with the polyclonal ETS2 antibody (Avivasysbio, CA, United States), washed by Phosphate buffer solution, then stained with secondary antibody (FITC-conjugated goat-anti-rabbit). Flow-cytometry (FC) assay was performed by BD FACS Calibur

flowcytometry (BD FACSCALIBUR™ FC-System, US) and the results were analyzed by Flowjo-7.6. software.

Data was analyzed by SPSS 18 (SPSS Inc, IL, United States) The Spearman and Pearson Correlation Coefficients were also performed. The, *P* value less than 0.05 was considered as significant[11].

The single cell based assay is an essential channel to unmask heterogeneity, diversity, and evolution. Besides, the high cell enumeration is required. There are automated apparatus, capable to automate, cell analysis, but very few cells is enummerated. Besides, through the manual analysis, broad exploration of multi thousand single cells are analyzable to unmask the new cellular function and their interaction.

PE has been assayed by

Manual single cell based analysis by IF, also based on high enumeration, with different magnification, which provides the classified intensity of the PE; Flow-cytometry (FC) which is totally machinery based and non- classified cellular screening according to the degree of intensity of the whole cell population with manual Immunofluorescence (IF), and FC.

Visions and visualization: PE assay and electoencephalography

The applied processes are performed according to the triangle style, by highlighting the power of cellular network, which reflects the association between the targets. PE of ETS2 is also performed in the peripheral blood of the patients with AD, according to the standard flow cytometry technique[11]. The PE assay was capable to unveil the nature of heterogeneity/diversity/course of evolution by exploring D1853N polymorphism in ATM gene, and PE assay of vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) at the single cell level of the brain and the course of evolution[12,13].

However, there are challenges regarding the CNCs in neurological disorders[14]. Furthermore, an innovative and complementary insight is required for an intensive

exploring of the brain channels as well. Buzsáki and colleagues have focused on "The origin of extracellular fields and currents — EEG, ECoG, LFP and spikes"[14]. Briefly, the challenges and achieved data in circulating tumor cells, and EEG highlights the involvement of two diverse territories and the related machinery in AD[14,15].

By considering the presence of family history of AD in the related pedigree; CNCs is offered as an applicable biomarker based test: (1) At any age, by only 2 mL of the pregnant maternal peripheral blood to screen the status of target embryo and/or fetus for ETS-2 gene and the circulating neural cells; and (2) screening the same test by buccal mocussa or buccal smear of the born child at different stages of his or her life. The combination of neurology/genetics/cell biology/psychology/ethics is required for the research and clinical management for the neurological disorders. Moreover, the following items harmonize the Personalized, Prognostics, Predictive, Preventive, predisposing strategiesl (5xP) by: (1) Applying the Genetic counselling by documenting the patients' pedigree, including the family history of the related diseases, at least, up to 3-4 or generations that are most informative; (2) Organization of the accustomed plan according to the psychological status of the referral cases; (3) Considering the macro-and/or micro-environmental factors in the patients' pedigrees; (4) Performing the required Genetics' analysis according to the information, based on the pedigree study; (5) Focusing on the apparently normal relatives, having the family history of the relatives affected with the diseases through generations in the pedigree; (6) Applying the required complementary test (s); and (7) Application of the predictive and early detective strategy for the target suspicious patients with AD and their target relatives.

Genetics/cell biology organize and play the most fundamental roles, by considering a triangle model to unmask the heterogeneity/diversity/evolution. Through such manner, the personalized diagnosis and therapy could be developed. AD as a major aim is selected to explore ETS2. This gene has been explored in two different group of patients affected with neuro-degenerative disorder including AD and Down's syndrome[11]. ETS2 with its pathogenic role, revealed different cellular behavior in two different diseases.

The results have suggested the strategy as 'Gene Product-Based Therapy (GPT)' and the personalized managements for both diseases.

RESULTS

PE assay

Analysis of PE was performed in the embryonic and chorionic villus samples; patients affected with AD. PE is assayed by IF in the peripheral blood samples and 1000-3000 cells were analyzed at single cell level, by the manual exploring. A sample of an aborted embryonic sample at the early gestational week has been explored to assay the mode of PE, including Neural marker (NE), neural stem cell (CD133) and vascular endothelial growth factor (VEGF) (Figure 1A). PE at early stage of embryonic period revealed to be high for neural marker (1A) and VEGF (1C) (Figure 1A). But, the Neural stem cell marker (CD133) is caharacterized with an absolutely lack of PE, which reflects no sign of stem cell function at early stage of embryo in this aborted sample (Figure 1A).

Regarding the chorionic villus, sample (CVS), the behavior of PE seems to be diverse, the highest PE is traced for VEGF with high angiogenesis in the whole sample (Figure 1B); mosaic pattern of PE for The neural marker (NE) is more remarkable (Figure 1B) than VEGF, the stem cell CD133, reveals a notable. Low expression, accompanied by few cells with high expression (Figure 1B) which reflect the initiative step for activation of CD133 stem cell, and significantly differs from the embryonic sample, lacking any expression of CD133. This is the course of evolution, which could be influenced by micro- and macro environmental factor during the fetal growth. Such behavior could occur for any other involved marker for cancer initiation and/or progression. By projecting the impact of early detection, the initial target to unmask any sign of functional alteration related to the neurological disorders including AD by circulating fetal cells (CFCs), is available. In this regard, we offer an extremely early detection of neural stem cell (CD133), ets2, and any related key proteins, involved in the initiation and progression of neurological disorders including AD at 8-9 gestational week (Figure 1B). Furthermore, screening the evolutionary course of the molecular and functional alteration (s) is possible by the

follow-up strategy and only 2-3 mL maternal peripheral blood as often as, is essential. In addition, we provide an early detective platform including the stem cells (CD133) at fetal period, *i.e.*, as early as 8-9 wk through the CFCs/chorionic villus (CVCs) in the maternal blood stream. Besides the key proteins including cyclins B, D, E, epidermal growth factors and vascular endothelial growth factor could be analysed. The benefit of such an extremely early screening is to deliberate the preliminary and preventive strategy including micro- and macro-environmental factors, counting nutrition. Besides, planning the essential and non-invasive screening, such as EEG at the right time through the offspring's life, under the guide and care of physician could be planned to detect any sign of AD manifestation (s) for applying any essential 5xP aims. Three proteins including ATM, ets-2 and VEGF are reflective of: (1) Weak expression of ATM as a tumor suppressor gene; (2) Mosaic pattern of PE for ets2; and (3) Remarkable expression of VEGF which is indicative of angiogenesis in the neural cells (Figure 3).

The CNCs were explored by IF method for combination of for neural marker, neural stem cell and angiogenesis (Ne/CD133/VEGF (Figures 4 and 5); and for Ne/CD133 (Figure 6). The PE of Ne/VEGF/ets2 is also provided (Figure 7). In addition, the CNCs were explored by IF method for combination of neural marker, neural stem cells and angiogenesis (Ne/CD133/VEGF (Figures 4 and 5). The migrated neural cells with High or low expression are shown with arrows. The micro-vesicle and the vascular section harboring the migrated neural cells are detectable. The CNCs were explored by IF method for combination of neural marker (Ne), neural stem cell for Ne/CD133 (Figure 6). The PE of Ne/VEGF/ets2 is also provided (Figure 7). Lower expression of this triangle (Ne/VEGF/ets2) is a reliable predictive/early and non-Invasive platform for exploring the status of AD at any stage of life. The CNCs' ratio, between pre- and post- intervention were analyzed based on the PE- screening of cytokeratin 19, and leukocyte common antigen (CD45) and epidermal growth factor (EGF). The cells conjugated with VEGF (Rpe), having lower expression (Figure 7), the CNCs' ratio, between pre- and post-intervention were analyzed based on the PE- screening of cytokeratin 19, and leukocyte common antigen (CD45) and epidermal growth factor (EGF). The personalized insight is

considered. The ratio value is estimated in cases. The Ratios are characterized as < 1 and > 1 between different channels within the horizontal and vertical axes. Finally, the diverse patterns were classified according to the distribution including clusters or sporadically forms. The CNCs' ratio, between pre- and post- intervention were analyzed based on the PE- screening of cytokeratin 19, and leukocyte common antigen (CD45) and epidermal growth factor (EGF) (Figure 8). The confirmation of CNCs was based on the mode of positive cytokeratin-19^{+} and negative CD45. The personalized insight is considered. The ratio value is estimated in cases. The Ratios are characterized as < 1 and > 1 between different channels within the horizontal and vertical axes. Finally, the diverse patterns were classified according to the distribution including clusters or sporadically forms.

Visions and visualization: PE assay and electoencephalography

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Applicability at a glance

The combination of neurology/genetics/cell biology/psychology/ethics is required for the research and clinical management for the neurological disorders. Moreover, the following items harmonize the Personalized, Prognostics, Predictive, Preventive, predisposing protocol (5xP) by: (1) Applying the Genetic counselling by documenting the patients' pedigree, including the family history of the related diseases, up to 3-4 or more generations; (2) Organization of the accustomed plan according to the psychological status of the referral cases; (3) Considering the macro-and/or micro-environmental factors in the patients' pedigrees; (4) Performing the required Genetics' analysis according to the information, based on the pedigree study; (5) Focusing on the apparently normal relatives, having the family history of the relatives affected with the diseases through generations in the pedigree; (6) Applying the required complementary test (s); and (7) Application of the predictive and early detective strategy for the target suspicious patients with AD and their target relatives.

Genetics/cell biology organize and play the most fundamental roles, by considering a triangle model to unmask the heterogeneity/diversity/evolution. Through such manner, the personalized diagnosis and therapy could be developed. AD as a major aim is selected to explore ETS2. This gene has been explored in two different group of patients affected with neuro-degenerative disorder including AD and Down's syndrome[11]. ETS2 with its pathogenic role, revealed different cellular behavior in two different diseases. The results have suggested the strategy as 'Gene Product-Based Therapy (GPT)' and the personalized managements for both diseases.

DISCUSSION

The information of patients' and controls are provided in Table 1 and Table 2. Total cells of 10000 in AD patients were analyzed by Flow-Cytometry (FC), but without providing any heterogeneity. The FC- results of ETS2, is provided (Figure 2). PE assay unmasked the nature of heterogeneity/diversity/course of evolution by exploring ETS2, D1853N polymorphism in ATM gene, vascular endothelial growth factor, epidermal growth factor and course of evolution at the single cell level of the brain**.** The arrangement of

Genetics/Cell biology/Psychology /Ethics is essential quadrat-radial format for programming the research and clinical management. The required steps in the Genetics and cell biological programs include (1) Genetic counselling/pedigree documentation; (2) Considering the macro-and/or micro-environmental factors; (3) Performing the required Genetics' analysis, based on the pedigree-information; (4) Considering the target proband's relatives for the required screening; and (5) applying the required Genetic test (s). Besides, harmonizing the 5xP insights are the essential targets in the clinics.

Complementary and comparative insights between different panels of PE assay is the key aim in the patients with AD PE of ETS2 by IF at analyzable single cell level of the AD patients are provided (Figures 3 and 8). However, PE is a challenging assay and the cells with high magnification are required to: (1) Reflect the clear panorama of the PE; and (2) Most importantly, to echo the cellular heterogeneity clearly. The PE of ETS2 is also assayed for then control individuals (Table 2). Two different single cell- based platforms are indicative of diverse conclusions. In fact, the most diagnostic and visibility of cellular diversity is achievable by IF through which the territory of the migrated cells from the brain domain is detectable (Figure 2 and 8). The provided figure by IF, clearly, reflect heterogeneity at single cell level.

An extra copy of ETS2 gene in the DNA of brain cells is reported by quantitative densitometry[16] and the provided guidlines[17,18] . Based on this valuable finding, the possible correlation of an extra chromosome 21 in DS as the cause of AD was also reported. In this regard, the expression of ETS2 was also high in Down's syndrome by: (1) A segmental trisomy model for transcriptome during postnatal development of DS in a mouse model[19]; (2) leading to induction of neural apoptosis[20]; and (3) high-expression of ETS2 Led to amplification of the APP gene expression and raising ß-amyloid proteins, with consequential brain anomaly in AD and DS[21] .The Most interesting report was related to the beta amyloid gene duplication in both Alzheimer's disease and the case of DS with normal karyotype[21]. It has been, also, emphasized that through the mechanisme of an imbalance process for gene dosage, the mental disorder could be evolved through

the molecular/cellular machinary in DS[22]. Conclusively, the ETS2 PE, as a remarkable pathogenic factor, has the fundamental role at single cell level of two different disease including AD and DS.

Frontal lobe functions and AD

As a major component of the cerebral cortex, the frontal lobe serves a variety of functions. It is believed that the orbital PFC and other ventromedial prefrontal cortex regions of frontal lobe play a significant role in the regulation of motivation and emotion[24,25]. The ventromedial PFC plays a more specialized function in pleasure, happiness, and reward conditioning[26]. Executive function, however, is one of the most significant frontal lobe-related functional groups. Executive functions are typically cognitive processes that help people tackle challenging, unique, and complicated tasks by choosing and fusing actions or thoughts with internal goals and mediating activities over time[27-29]. Working memory, cognitive flexibility, and inhibition are all components of executive function, which is reliant on top-down (*i.e.*, goal-driven) control of distributed processes taking place across the brain. The nature of the processes being controlled determines the precise behavioral output[30]. Key cognitive processes relating to social, emotional, and motivational elements of conduct are carried out by prefrontal cortical areas. Working memory, goal-driven attention, task switching, planning, problem-solving, and the need for novelty are all functions of the dorsal lateral prefrontal cortex. The medial prefrontal cortex is involved in self-awareness, motivation, emotional regulation, and updating goal-directed behavior; the orbitofrontal cortex is involved in personality, inhibition, and emotional and social reasoning. The ventral lateral prefrontal cortex is involved in inhibition, response selection, and monitoring[27]. Dysexecutive syndromes have historically been linked to dorsolateral prefrontal cortex damage, but it is now understood that they can also be caused by a parietal-temporal-frontal system impairment, which is the focus of a specific type of atypical AD. Simple daily tasks requiring executive control and a variety of neuropsychological tests are among the tasks that this dysexecutive Alzheimer phenotype performs poorly on. Disrupted executive

control over social, emotional, and motivational elements of behavior characterizes dysexecutive syndromes, which are more closely associated with the frontal lobe[31].

EEG findings in AD

It is crucial to take into account both the rhythms' location in the brain during EEG analysis in addition to the rhythms themselves. For instance, because alpha rhythms represent the activity of several neuronal populations, they have different neurological correlates when they are observed in the occipital, temporal, or frontal cortexes[32].

The majority of EEG studies used to diagnose AD have been based on spectral decomposition of scalp signals in both the resting state with closed eyes and open eyes. We now understand that healthy aging causes changes in brain activity, which are consequently recorded in EEG recordings. They include an increase in delta (1-4 Hz) and theta (4-8 Hz) power, a decrease in background activity, and a slowing of alpha activity (8-13 Hz)[33]. During physiological aging, the magnitude of the alpha rhythm reduces in posterior cortical regions, and this is related to the level of general cognitive function[34]. However, numerous studies indicate that compared to age-matched controls, both MCI and AD suffer from changes in the pattern of their EEG recordings: Alpha and beta rhythms typically decline, whereas delta and theta oscillations generally increase[35-37]. At the start of the AD, there is an increase in slow waves, notably in the theta rhythm. The earliest indicators of cognitive deterioration and the theta power rise are related[38]. theta relative power, (which is expressed as the percentage of theta band power to all other bands), is higher in AD than in MCI and higher in MCI than in healthy controls and is associated with worsening performance across all cognitive domains[39]. alpha power is lower in AD than in MCI, and in MCI than in normal people[40]. There is a correlation between the decline in alpha activity and the severity of the illness and the cognitive abnormalities[40]. In addition to spectrum features, EEG also has synchronization features. EEG synchronization also describes how various brain oscillations are adjusted. When two distinct signals lock in phase, become phase-amplitude coupling, or modulate their amplitudes simultaneously (amplitude-amplitude coupling), they are said to be

coupled[41]. One of these is spectral coherence measurement, which measures the spectral covariance of activity between two electrode locations. When compared to healthy controls, EEG coherence in AD participants exhibited statistically significant changes[42-44]. Alpha wave coherence in the temporo-parieto-occipital regions decreased in AD patients, although delta wave coherence between the frontal and posterior regions increased[45]. Considering the previously mentioned theory that basal forebrain neurons are severely impaired, all EEG characteristics associated with AD, such as changes in frequency patterns and synchrony measurements, may be caused by the loss of neurons, altered anatomical structure of the neuronal tracts, as well as altered release of neurotransmitters, all of which lead to impairments in neural activity[44].

Highlighted points of view

Neurological disorders are extremely complicated with an influential impact on the whole society including the patients' family and close friends. Therefore, the educational packages are required to create the cooperative surrounded living atmosphere between the patients, family and the friend.

Regarding the muti-dimentional approach of the neurological disorders, including AD, the following facts and directive points of view in the recent review article provided by Tanaka and Vécsei (2022)[46]: Differentiating the "neuroprotective and neurodegenerative modules of neurological and neuropsychiatric diseases", highlighting the etiology, available techniques, diagnostic and therapeutic approaches. of neurodegenerative diseases.

As the whole, neural engagements can be stabilized by the" neuroplasticity" which is characterized by: (1) The nervous system capabilities to convert other components; (2) Based on the status of functions, structural format, and constructive ability; and (3) being malleable, tolerative and adaptive against the non-desirable event and challenges[46].

CONCLUSION

Application of CNCs and correlated Ratio based between Brain channels by providing the 5xP personalized clinical management model for early detection and therapy of the patients with AD and their targeted/predisposed relatives. Highlights offer an early detective platform by considering neuro-Genetics/cell Biology, Circulating Neural Cells; molecular investigation, for the) predisposed individuals to AD- or other neural disease. The initiation and functional stage of triangle PE including neural- marker, stem cell (CD133), and vascular endothelial growth marker (VEGF) is unmasked not at the embryonic pahse, but through the beginning of chorionic villus period around 10^{th} gestational period. The mediation with LM resulted to remarkable escalation of the power of alpha band wave at frontal lobe including Fz, F4, FC2 sites, Cz in central lobe and O1 in occipital lobe. The increased activity of Alpha waves in Centro-frontal regions.

ARTICLE HIGHLIGHTS

Research background

Circulating Neural Cells (CNCs) is an essential strategy which offers the *pentagonal* application including the Personalized, Prognostics, Predictive, Preventive, predisposing (5xP) panel in the clinical neurology and Neuro-Science. Therefore, it was aimed to explore the developing picture of CNCs' behavior of the brain cells in the blood stream. CNCs are an available approach for the preventive Medicine and the personalized/target- basic therapy

Research motivation

This strategy include and offers: (1) Routinizing the CNCs assay through the high and reliable enumeration of the CNCs; (2) Providing the required information's of CNCs to the Neurological clinics for the patients affected with neurological disorders including Alzheimer disease; (3) Providing adequate Information on the application of CNCs for the protocol to the target clinical centers for either their referral patients affected with, or predisposed to AD as promtly as possible; (4) Highlighting the safety, rapidness of the process, non-invasiveness of the CNCs exploration; and an early/preventive strategic

detection of the AD in the probands and the relatives through their pedigree; And (5) Considering the pedigree-based analysis for tracing of any micro- and macro-environmental predisposing factors, including nutrition and the history of the neurological based diseases including AD.

Research objectives

In the Alzheimer-prone families, the history of any related clinical sign of the neurological symptoms including light and/or progressive through different generations of the referral suspicious case, could be candidatef for exploring CNCs. If there is any persuasive micro-and/or macro-environmental risks, the target of the proband's offspring may be candidate for the CNCs.

Research methods

The originality of the provided research is based on the Manuel performance and exploration of the single cell based analysis with high enumeration. This strategy is capable to unmask the heterogeneity, diversity and highlights the specific role of the target proteins, and identification of the novel involvement of additional protein through the developmental stages of AD. Furthermore, by respecting the bridging system between Medicine and Science, and according to the primary results of Electroencephalography, as a golden performance, an innovative, complementary and predictive model is provided in this paper. Finally, based on an early detection, and the developmental process through the passed progressive period of AD, the personalized detection, hopefully, leads to the personalized therapy.

Research results

The novel results of the provided manuscript are characterized with: Personalized data; Single cell based strategy; and translatable data for the index case and their relatives;

An early detection of the protein expression (PE) and brain channels bridging systems, the personalized therapy, could be translated, either for Alzheimer or the related psychological related to the brain disorders

Research conclusions

Unmasking the diverse pattern of PE of the migrated cells from brain to the blood stream, by an adequate enumeration of the CNCs based on the Manuel Analytical approach (MMA). Unveil the heterogenic pattern of the analyzed target proteins' expression.

Research perspectives

Unmasking the role of other candidate protein (s). Considering the Informative publication (s) as the complementary educational package. Bridging between Science and Medicine by considering the pedigree based translational system for neuro-model, as an early detection platform. Suggesting for stablishing the Neuro-clinic with the aims including 'Personalized- Predictive/Early detection/ Preventive clinic for the families with 'Alzheimer disease' and in future with neuro-genetics disorders'.

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