Journal of Neurology, Psychiatry and Brain Research

Kosmos Publishers

Review Article

Jou Neu Psy Brain. JNPB-105

Morphopathological Changes of Dendrites in the Edematous Human Cerebral Cortex

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Citation: Castejón OJ (2018) Morphopathological Changes of Dendrites in the Edematous Human Cerebral Cortex. Inte Jr Neuro and Neuroscie: IJNANS-105.

Received Date: 13 August, 2018; **Accepted Date:** 30 August, 2018; **Published Date:** 10 September, 2018

Abstract:

Swollen and beaded dendrites exhibit fragmentation of limiting plasma membrane, cytomembranes and cytoskeletal structures. The swollen dendrites show vacuolization, dense residual bodies, enlarged rough and smooth endoplasmic reticulum, and edematous clear and dark mitochondria. The multifactorial processes associated with brain edema and brain ischemia, such as calcium overload, activation of calcium-dependent proteolitic enzymes, protein aggregation, glutamate-induced neurotoxicity, release of lysosomal enzymes, deficit of ATP, stress oxidative and lipid peroxidation have been considered in relation with pathological dendritic changes. Dendrotoxicity due to brain edema and brain ischemia seems to be the fundamental pathogenetic mechanism underlying the dendritic damage.

Keywords: Brain Edema; Brain Trauma; Brain Tumors; Electron Microscopy; Dendrites; Hydrocephalus

Introduction

Dendritic development and arborisation show aberrant or anomalous patterns in aging process and various central nervous system diseases, such as brain trauma, neurodegenerative diseases, epilepsy, malnutrition in developing brain, infections, mental retardation, hydrocephalus, cerebral ischemia, and exposure to alcohol and other toxins **[1-29]**. The formation of meganeurites in human neuronal storage diseases **[4,9]**, the existence of more branched dendrites in neuronal elderly individuals **[2,30]**, and the appearance of new dendritic growths in Alzheimer disease **[1]**, reveal that the adult human neuronal system appears capable of responding to various stimulus, and exhibits the potential to modify existing neuronal connections. Abnormal dendritic development and dendritic spine "dysgenesis" have been reported in mental retardation **[17,31]**, and severe protein-calorie malnutrition **[16]**. Aberrant dendritic growth and aberrant patterns of spine morphology have been reported by Machado-Salas (1984) **[32]** in Bourneville's disease. Marked atrophy of basal and apical dendrites of neurons of layer 3 and 5 of cerebral cortex in Tay-Sachs disease was reported by Takashima et al. (1985) **[33]**. Loss of

Purkinje cell spines, cactus-like thickenings and atrophy of Purkinje cell dendrites may be found in Menke´s disease **[34]**, and in experimental encephalopathy induced by chronic application of valproate [**22]**. Abnormalities of dendritic arborization have been observed by light microscopy in a variety of cerebral malformation, such as microgiria and lisencephaly **[9]**.

In epilepsy a wide spectrum of dendritic pathology has been recognized, such as loss of dendritic spine and development of nodular or fusiform enlargements along the dendritic shafts **[19,24]**. Dendritic abnormalities have been also described in normal aging and various dementias **[5,30]**. Normal elderly individuals have longer and more branched dendrites than younger and senile dementia patients **[1,35,36]**. Abnormal dendrites have been also found in Huntington´s disease **[37]**. Age-related regulation of dendritic endocytosis was reported by Blanpied et al. (2003) **[38]**. Castejón and Arismendi (2003) described swollen and beaded dendrites, disrupted limiting plasma membrane and cytoskeletal structures in the human edematous cerebral cortex associated to brain trauma, congenital malformations, and brain tumors. Works et al. (2004) **[39]** reported age-dependent dendritic atrophy of basilar dendrites in the rat nucleus magnocellularis related with loss of cholinergic innervation. Vega et al. (2004) **[40]** described increased dendritic length, and decreased density of synaptic spines in the prefrontal cortex of rat with renovascular hypertension. Allred and Jones (2004) **[27]** found dendritic structural plasticity after unilateral ischemic damage of rat sensory motor cortex. Wedzony et al. (2005) **[41]** reported diminished length of basilar dendrites of prefrontal pyramidal neurons in adult rats after blockade of NMDA receptors in the postnatal period. Rensing et al. (2005) **[42]** described dendritic swelling and loss of spines during electrographic seizures induced by 4-aminopyridine in transgenic mice. Peyghambari et al. (2005) **[28]** described a significant reduction in the length of most dendrites in the axotomized motoneurons of the spinal cord in newborn rats. Radley et al. (2005) **[43]** encountered reversible apical dendritic retraction in the rat medial prefrontal cortex following repeated stress. Brown et al. (2005) **[44]** also found remodelling of apical dendrites, atrophy of distal branches, and sparing of proximal branches induced by stress in medial prefrontal cortex. Flores et al. (2005) **[29]** reported decreased length of basilar dendrites in post-puberal rats after nenonatal excitotoxis lesions of the ventral hippocampus. Zaja-Millatovics et al. (2005) **[45]** demonstrated shortened dendritic length of neostriatal medium spiny neurons in Parkinson disease. Ishikura et al. (2005) **[46]** described dendritic atrophy in prion disease. Diersen and Ramakers (2006) **[47]** emphasized the dendritic pathology in mental retardation from the genetic point of view. Shimada et al. (2006) **[48]** studying a model of cerebral degeneration, the ageing SAMP10 mouse, described age- related dendritic retraction in the entire cerebral cortex and olfactory bulb. Brief exposure to excitotoxic agonists can result in substantial loss of the microtubule-associated protein MAP2 from neuronal dendrites, and accumulation in somata. A possible mechanism underling MAP2 loss is the activation of the calcium-dependent protease calpain by excessive dendritic Ca2+-loading. Baloyannis et al. (2007) describe substantial alteration of dendritic arborisation in the acoustic cortex in Alzheimer's disease. Chenet al. (2010) analized the immediate changes following acute cortical compression. Compression instantly twisted the microtubules and deformed the membrane contour of dendritic trunks, and immediately reduced dendritic spines on the entire dendritic arbor.

According to Martin and Wellman (2011) **[49]**, glucocorticoid stress hormones target medial prefrontal cortex (mPFC) and either chronic stress or chronic administration of glucocorticoids produces dendritic remodeling in prefrontal pyramidal neurons. Tan et al. (2012) demonstrated that peripheral nerve injury induces Rac1-regulated remodelling of dendritic spines on dorsal horn neurons, and suggested that this spine remodelling contributes to neuropathic pain. Essential Tremor (ET) is among the most prevalent neurologic disorders. Growing clinical and neuro-imaging evidence implicates cerebellar dysfunction in the pathogenesis of ET and emerging postmortem studies have identified structural changes in the cerebellum, particularly in Purkinje cell dendritic swellings **[50]**. In the present review we analyze at submicroscopic level the dendritic morphological changes of nerve cells in the edematous human cerebral cortex associated to congenital hydrocephalus, brain trauma, and brain tumors, in an attempt to provide better insight on the pathological changes induced by these distinct nosological entities, and the associated brain ischemia.

Sub microscopic Changes of Dendrites in Congenital Hydrocephalus

The immature hydrocephalic cerebral cortex neuropil in neonate patients with congenital hydrocephalus shows irregularly beaded shaped, and swollen and vacuolated dendritic processes with elongated and dark mitochondria. These dendrites exhibit mushroom, stubby and filipodic types of dendritic spines making asymmetric synaptic junctions **(Figure1)**.

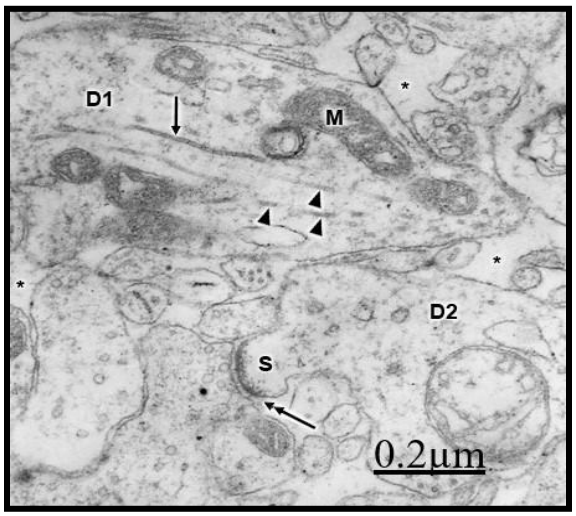

Figure 1: Arnold-Chiari malformation and communicant hydrocephalus. Neuropil of a 10 days-old neonate. Rigth parietal cortex. High magnification of a swollen and clear dendrite (D1) exhibiting dark swollen mitochondria (M) with clear dilated cristae, and intact (long arrow) and few fragmented microtubules (arrowheads). A neighboring clear dendrite (D2) shows an asymmetric synaptic contact (double head arrow) by means of mushroom type-dendritic spine (S). The asterisks label the enlarged extracellular space.

Most patients with congenital hydrocephalus exhibit lamellipodic and filopodic dendritic processes, and endocytic vesicle formation at the limiting plasma membrane. Some dendritic processes show fragmented plasma membrane in areas of severe brain edema **(Figure 2)**.

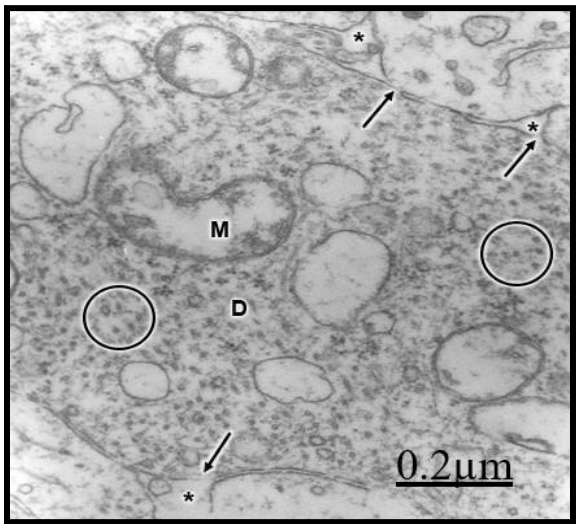

Figure 2: Congenital hydrocephalus associated with lumbar meningomielocele. Right parietal cortex. Neuropil of a 12 days-old neonate showing the longitudinal section of an edematous dendritic process (D) showing a clear dendroplasm, swollen mitochondrion (M), cross sectioned microtubules and neurofilaments (circles). The long arrows label the disrupted dendritic plasma membrane. Note the dilated extracellular space (asterisks) surrounding the dendritic profile that features hydrocephalus interstitial edema.

Mc Allister et al. (1985) **[51]** reported dendritic varicosities and spine loss as the most striking dendritic alterations in experimental induced hydrocephalus in newborn rats. Harris et al. (1996) **[52]** found a decreased in the total length of dendritic tree in the infant H-TX rats. Hydropic dendritic deterioration has been reported in feline-infantile hydrocephalus by Kreibel and McAllister (2000) **[53]**.

1.1. Dendrite Pathology in Human Traumatic Brain Injuries

In patients with traumatic brain injuries exhibiting contusions and associated subdural or extradural hematoma or hygroma, varicose swollen dendrites with fragmented plasma membranes, disruption of cytoskeletal structures characterized by disintegrated microtubules and neurofilaments, electron lucid and vacuolated dendroplasm, enlarged rough and smooth endoplasmic reticulum, partial loss of dendritic spines, increased vesicular transport of microvesicles, dense round and elongated inclusion bodies, and

complex or clathrin-coated vesicles are observed **(Figures 3&4)**.

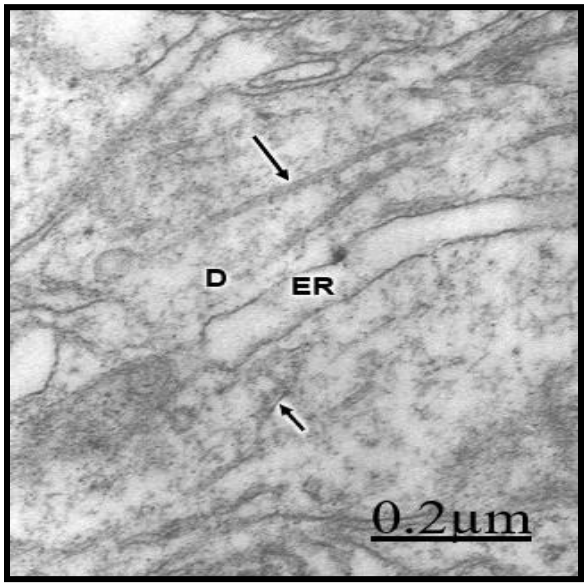

Figure 3: Brain trauma. Severe contusion of frontal region. Left frontal cortex. Swollen shaft dendritic segment (D) displaying dilated smooth endoplasmic reticulum cisterns (ER), and intact (long arrow) and fragmented microtubules (short arrow).

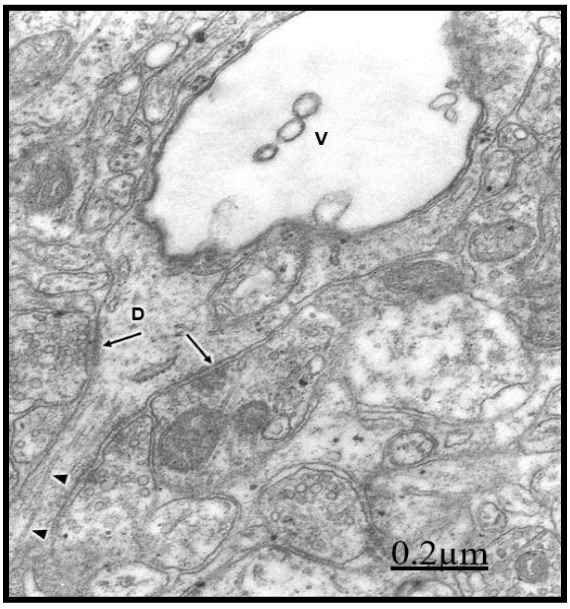

Figure 4: Brain trauma. Contusion and facture of frontal region. Left frontal cortex. Beaded dendrite (D) showing a huge vacuole (V), microtubules (arrowheads) and activated asymetric axodendritic synapses (long arrows) are seen in the initial dilated segment.

Dendritic angulations, and nodular or segmentary dendritic swelling were earlier reported by Vaquero et al. (1982) **[54]**, Gallyas and Zoltay (1992) **[10]** and Swann et al. (2000) **[19]** in human epileptic dendrites. According to Vaquero et al. (1982), the nodular dendritic swellings are due to alteration in the microtubular arrangement. Vacuolated dendrites inducing hydropic deterioration and degeneration of dendrites have been reported by Goldstein et al. (1983) **[6]** in rat central nervous system after ethanol consumption, by Posmantur et al. (1996b) **[55]** after traumatic brain injury in rats, and by Sobaniec-Lotowska (2001) **[22]** in rat experimental encephalopathy induced by valproate. Saito et al. (1990) **[56]** found calcium accumulation in swollen dendrites following cerebral ischemia and traumatic brain injury. Gallyas and Zoltay (1992) **[10]** considered that in the cases of head injury, the beaded appearance of dendritic and axonal processes indicates an advanced stage of morphopathological damage. In addition, some neurons exposed to hypothermia, NMDA or ionophore also developed beaded dendrites **[57]**. Focal dendritic swelling was observed by Ferrer et al. (1998) in mucopolysaccharidoses types I, II and III. The focal swelling of dendrites is apparently similar to that observed in axonal processes also due to destruction of cytoskeletal network **[58]**. Swollen and beaded dendrites have been widely reported in a large variety of pathological entities. Dendritic swelling was observed in stroke-prone spontaneously hypertensive rats **[59]**, following intrathecal infusion of N-methyl-D-aspartate, in rats with neuroleptic-induced dyskinesias **[60]**, and in rat brain during acute focal ischemia **[20]**. Swann et al. (2000) **[19]** postulated an ongoing excitotoxic injury of dendrites (dendrotoxicity) produced by excessive release of glutamate especially during seizures. In brain trauma there is also glutamate-induced citotoxicity **[61]**, which supports Swann et al. (2000) **[19]** hypothesis. According to Hasbani et al. (1998) **[62]**, the postsynaptic neuronal dendrite is selectively vulnerable to hypoxic-ischemic brain injury and glutamate receptor overactivation. Sodium, chloride, and water entry contribute acutely to excitoxicity dendritic injury, and calcium entry through NMDA receptors results in lasting structural changes in damaged dendrites. Lately Hasbani et al. (2001) **[21]** expressed that in cerebral ischemia; neurons exposed

to NMDA, kainite or oxygen-glucose deprivation suffer dendritic beading and lost of dendritic spines.

Lee et al. (1991) **[63]** point out that Ca^{++}-activated degradation of cytoskeletal proteins appears to be an early and important component of the post-ischemic response in hippocampal neurons, which can contribute to neuronal death. According to Tomimoto and Yanagihara (1994) **[64]**, the disintegration of microtubules and the resulting disruption of dendritic transport may contribute to subsequent development of delayed neuronal death. The molecular mechanism inducing the disintegration of cytoskeletal structures in traumatic brain injury could be due to loss of cytoskeletal proteins and microtubule associated protein 2 (MAP2), possibly by calpain-mediated proteolysis **[55,65]**. Brain contusions also induce loss of both, MAP2 and neurogranin immunoreactivity **[66]**. Mild and repetitive brain injuries may trigger cytoskeletal alterations related to neuronal degeneration and abnormal behavior **[67]**. Cytoskeletal disruption is a key pathological feature of Alzheimer's disease, characterized by dendritic degeneration **[5,68]**. Ultrastructural abnormalities of dendrites with damage of endoplasmic reticulum, mitochondrial lesion and disintegration of microtubules have been observed after chronic administration of valproate **[22]**. Similar dendritic changes have been recently observed after fluid perfusion injury **[69]**.

Our findings suggest that anoxia e ischemia are the major pathogenetic mechanisms of dendritic swelling in the edematous human cerebral cortex associated to brain trauma, tumours and congenital malformations. Our observations on dendritic abnormalities in brain traumatic injuries revealed predominant beaded shape of swollen dendrites in comparison with those seen in brain malformations and tumors. The beaded dendrites exhibit disintegrated microtubules and microfilaments mainly at the dendritic varicosities. Derangement of dendritic cytoskeletal structures, mainly fragmentation and disintegration of microtubules and neurofilaments, are due to multifactorial factors, such as the shear stress induced by the traumatic agent, mitochondrial swelling, anoxic-ischemic condition of brain tissue, and protease activation.

In relationship with the damage of the limiting plasma membrane and the dendritic cytomembranes, such as mitochondrial, rough and smooth endoplasmic reticulum, lysosomal and Golgi membranes, could be due to increased permeability of lysosomes and release of acid and neutral proteases **[70,71]**, interruption of dendritic transport **[64]**, calpain-mediated spectrin breakdown **[72]**, free radical release and lipid peroxidation **[73-75]**, delayed phospholipid degradation by phospholipase activation **[76]**, disruption of cytoskeletal structures, mitochondrial abnormalities and impaired production of ATP, elevation of intracellular calcium **[56,57]**, activation of calcium-dependent proteolitic enzymes glutamate-induced neurotoxicity **[19,75,77]**, protein aggregation after brain ischemia and reperfusion **[78,79]**, intensity of shear forces in brain traumatic injury, increased intracranial pressure in moderate and severe edema, and release of lysosomal enzymes **[13,80]**.

Dendritic Abnormalities in Brain Tumors

In relationship with the alteration of dendritic processes in brain tumors, such a cystic craniopharyngioma and ependymoma, we have observed swollen dendrites with a granular proteinaceous aggregation in the dendroplasm, vacuolated rough and smooth endoplasmic reticulum canaliculi, dark and clear swollen mitochondria, disintegrated neurofilaments, scarce amount or absent of microtubules, presence of clathrin-coated vesicles and myelin-like figures **(Figure 5)**.

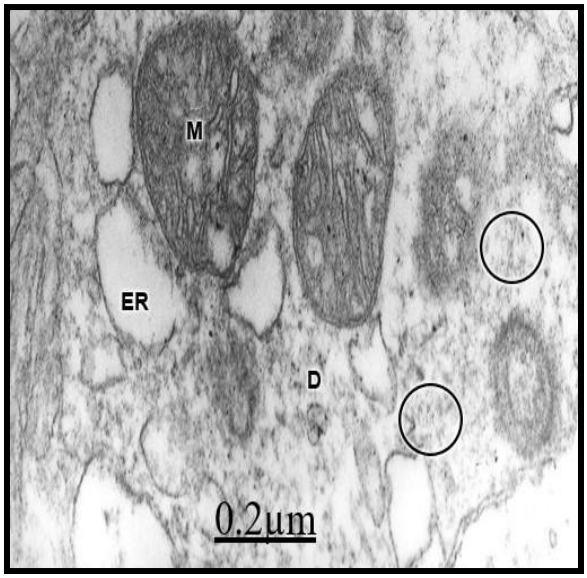

Figure 5: Cystic craniopharyngioma. Right fronto-temporal cortex. Severe edema. Clear swollen dendrite (D) containing dark edematous mitochondria (M) and vacuolization of smooth and rough

endoplasmic reticulum (ER). Microtubules and microfilaments appear disintegrated giving to the dendroplasm a granular aspect (circles).

Swelling of dendrites with disarray of microtubules and neurofilaments and changes of surface morphology of dendritic spines were earlier reported by Spacek (1987) **[81]** in epitumorous cerebral cortex.

Concluding Remarks

Swollen and beaded dendrites exhibit fragmentation of limiting plasma membrane, cytomembranes and cytoskeletal structures **[82-87]**. The swollen dendrites show vacuolization, dense residual bodies, enlarged rough and smooth endoplasmic reticulum, and edematous clear and dark mitochondria. The multifactorial processes associated with brain edema and brain ischemia, such as calcium overload, activation of calcium-dependent proteolitic enzymes, protein aggregation, glutamate-induced neurotoxicity, release of lysosomal enzymes, deficit of ATP, stress oxidative and lipid peroxidation have been considered in relation with pathological dendritic changes **[88-91]**. Dendrotoxicity due to brain edema and brain ischemia seems to be the fundamental pathogenetic mechanism underlying the dendritic damage.

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1. Keywords

Chiropractic, history, mental health, vertebral subluxation, manipulation, depression, anxiety, addiction, hospitals, autonomic nervous system, biological oscillators, neuroplasticity, polyvagal theory, neurovisceral integration, heart rate variability, resiliency, adaptability, salutogenesis

2. Introduction

Musculoskeletal conditions are the predominant reason persons seek chiropractic care. The top five reported reasons for attending chiropractic care are low back pain/back pain, neck pain, extremity problems, wellness/maintenance and hip pain. The top five reasons for pediatric cases to attend chiropractic care are musculoskeletal conditions, excessive crying, neurological conditions, gastrointestinal conditions, and ear, nose, and throat conditions **[1]**. Although many chiropractors and those they serve tend to focus on disorders associated

with the physical body, abnormal nervous system function may also affect emotional and psychological health. The author completed a brief historical overview of chiropractic and mental health **[2]**. This work represents expansion of that paper, and inclusion of putative neurobiological mechanisms.

3. History

D.D. Palmer founded the chiropractic profession 123 years ago. He described vertebral subluxations as "slightly displaced vertebrae which press against nerves causing impingements, the result being too much or not enough functioning" **[3]**. According to his son, B.J. Palmer, "D.D. Palmer was the first man to discover that insanity was caused by displaced cervical vertebrae, that by replacing them the patient could be restored to normal condition" **[4].** B.J. also described his expert testimony in a case where he stated, "If an atlas is subluxated it makes abnormal the functions of the brain." In answer to the question, "What is to be done in insanity?" he admonished his reader to "Go back to cause. Adjust that and return that brain to its normal capacity and capability" **[5]**. Another pioneer in the field of mental health and chiropractic was attorney and chiropractor Willard Carver. Carver authored the book, Pyscho-Bio-Physiology, and wrote, "Between the Psychology and the Physiology I have built the Biologic bridge that scientifically connects these two very important departments of human experience" **[6]**.

In the 1920s, several inpatient mental health facilities were established where chiropractic adjustments were the dominant clinical service provided. Two of these were located in Davenport, Iowa. In 1922, the Chiropractic Psychopathic Sanitarium was established. The facility was later known as Forest Park Sanitarium. North Dakota Judge A. W. Ponath noted that at the North Dakota state mental hospital, the "cure and discharge rate" ranged from 18-27%, compared to 65% at Forest Park **[7]**. The second facility, Clear View Sanitarium, was established in 1926. In 1951, Clear View was acquired by the Palmer School of Chiropractic. Chiropractor W. Heath Quigley, who directed the sanitarium, described the clinical protocol: "Each day, each patient was examined with the neurocalometer (NCM). If the clinician interpreted the NCM to indicate nerve impingement, the patient was adjusted." Quigley reported that the rooms were "sunny and bright," and that meals included "large servings of fresh vegetables...from a garden" **[8]**. Unfortunately, both institutions closed, (Forest Park in 1959 and Clear View in 1961) in large measure because of third party pay issues. Insurance companies often refused to pay the costs of care. Furthermore, Iowa statutes at the time did not provide for licensing specialized hospitals; only full service medical hospitals were eligible for licensure. Clear View was not licensed as a hospital, and functioned legally as a nursing home **[9]**.

The 1970s saw a renewed interest in chiropractic care and mental health issues. In 1973, Chiropractor Herman S. Schwartz edited a book titled "Mental Health and Chiropractic: A Multidisciplinary Approach." Contributors included Nobel Laureates Rene Dubos and Linus Pauling, and such notables as Scott Haldeman, A.E. Homewood, Joseph Janse, Alexander Lowen, and Thomas Szasz **[10]**. In 1949, Schwartz had published a preliminary report of 350 patients afflicted with a "nervous or mental disorder" and reported that the majority of them showed improvement under chiropractic care **[11]**. Schwartz was active in the ACA Council on Mental Health (formerly Council on Psychotherapy), which survived through the '70s, but no longer exists. In 1983, Quigley authored an article describing a four decades period where "treatment of the mentally ill was a highly motivated discipline within the chiropractic profession" **[12]**. In 1988, Goff wrote a review of the theory and practice of "chiropractic treatment for mental illness" **[13]**. Interest in this field continues. Blanks, Schuster and Dobson **[14]** published the results of a retrospective assessment of subluxation based chiropractic care on self related health, wellness and quality of life. This is, to the authors' knowledge, the largest study of its kind ever undertaken regarding a chiropractic population. After surveying 2,818 respondents in 156 practices, a strong connection was found between persons receiving Network Spinal care (a chiropractic technique) and self reported improvement in health, wellness and quality of life.

A systematic review was published which examined psychological outcomes in randomized controlled trials of spinal manipulation The study concluded that "There was some evidence that spinal manipulation improved psychological outcomes compared with verbal interventions…The clinical implications are that physical treatments, such as spinal manipulation have psychological benefits" **[15]**. Genthner et al **[16]** reported on a series of 15 patients with a history of depression. The Beck Depression Inventory II (BDI-II) was used to measure the baseline level of depression and any post-chiropractic care changes following orthospinology care, a chiropractic technique focused on correcting misalignments of the craniocervical junction. A paired t-test demonstrated significant improvement in depression test scores. A study evaluating the role of chiropractic care in persons undergoing inpatient addiction care consisted of a three arm randomized clinical trial with two control groups (one receiving usual medical care, and the other placebo controlled). This was a single blind study utilizing subluxation-centered chiropractic care, Torque-Release technique, implemented in a residential addiction care setting. The active group showed a significant decrease in anxiety while the placebo group showed no decrease in anxiety **[17]**. Other articles addressing mental health issues and chiropractic care have been published, ranging from single case reports to randomized clinical trials. Favorable responses were reported in persons with conditions including depression **[18]**, ADHD **[19]**, autism **[20]**, dyslexia and learning disabilities **[21]**. Additionally, published papers report changes in general health measures in chiropractic patients using the RAND-36 and Global Well Being Scale (GWBS) **[22]**, changes in domains of health related quality of life among public safety personnel undergoing chiropractic care **[23]**, and chiropractic care in patients with cancer-related traumatic stress symptoms **[24]**.

4. Salutogenesis

Chiropractic care incorporates a salutogenic approach. Sociologist Aaron Antonovsky coined the term salutogenesis in 1979. It is derived from salus, Latin for health, and genesis, meaning to give birth. Salutogenesis, the study of the origins and creation of health, provides a method to identify an interconnected way to enhance well-being. Salutogenesis provides a framework for a method of practice to promote health **[25]**.

Salutogenic theory goes to the very essence of neurobiology. It has been noted that neurological processes (as well as anatomical structures) are remodeled by sensory input. These processes, collectively termed neuroplasticity, are operative at all levels of the nervous system. Smith **[26]** described the range of these mechanisms: "From the afferent (incoming) activity of peripheral sensory receptors to the efferent (outgoing) activity directed toward neuroendocrine organs, blood vessels, and muscles. Although the selectivity of perception probably makes it impossible to be aware of everything that is happening throughout the body, it is evident that these regulatory processes are essential for one's health, and that they provide the basis for functional salutogenic mechanisms of the brain." Smith further noted, "An organism with a salutogenic brain would experience the world as manageable and coherent ... with a self-perpetuating cycle for enhancing self-confidence and well-being."

5. Stress Responsivity

Hans Selye **[27]** pioneered investigations of the biological effects of stress in 1936 with the publication of his paper, "A syndrome produced by diverse noxious agents." Since then, more than 100,000 articles and books have been written on the subject. Selye describes stress as the nonspecific response to any demand. Although many individuals have concluded that stress is inevitably destructive, this view is incorrect. Selye noted, "Stress is not necessarily bad for you. It is also the spice of life, for any emotion, any activity causes stress...the same stress that makes one person sick is an invigorating experience for another...Complete absence of stress is incompatible with life since only a dead man makes no demand on his body or mind." Selye described two types of stress: Dis-stress -- from the Latin "bad," as in dissonance, and Eu-stress from the Greek "true" or "good," as in eutonia. Whether we experience a pleasant or unpleasant result from an event depends upon how our nervous system perceives, processes, and interprets that event. More than 15 years before

Selye's historic publication, B.J. Palmer and J.H. Craven **[28]** described a similar concept: concussion of forces. This term refers to the meeting of external invasive forces and internal resistive forces. Just as stress may be destructive or beneficial, concussion of forces may produce or reduce vertebral subluxation. The result is dis-ease or ease. "That which caused the normal cycle to become abnormal was a concussion of forces centering at some point in the spinal column causing a subluxation...tissues do not nor cannot express their normal function." Palmer **[29]** quotes Webster's definition of adaptation: "To make suitable; to fit; or suit; to adjust; alter so as to fit for a new use." More than 60 years later, Selye **[30]** wrote, "Every living being has a certain innate amount of adaptation energy or vitality." When a concussion of forces is corrective, Palmer **[29]** noted the following changes: "Perversion changed to verification; abuse to proper natural use; abnormal interpretation to normal interpretation; distortion to healthful manifestation; corruption to correction." Although it is unlikely that Selye was familiar with the writings of Palmer and Craven, the similarities are striking: Stress and concussion of forces; eu-stress and ease; dis-stress and disease. The practical application of these concepts requires a working definition of health. The World Health Organization (WHO) **[31]** defines health as "A state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity." In this context, Selye **[30]** wrote, "The secret of health and happiness lies in successful adjustment to the ever-changing conditions on this globe; the penalties for failure in this great process of adaptation are disease and unhappiness."

6. Putative Neurobiological Mechanisms

6.1. Vertebral Subluxation

In 1906, DD Palmer and BJ Palmer **[32]** defined subluxation as follows: “A (sub)luxation of a joint, to a chiropractor, means pressure on nerves, abnormal functions creating a lesion in some portion of the body, either in its action, or makeup”. Lantz **[33]** noted, “Common to all concepts of subluxation are some form of kinesiologic dysfunction and some form of neurologic involvement”. Mechanical and degenerative changes associated with vertebral subluxation may result in a variety of neurological consequences:

- **Cord compression and adverse cord tension:** Compression of the spinal cord may result from disc protrusion, ligamentum flavum hypertrophy/corrugation, or osteophytosis. Myelopathy may result in cord pressure and/or pressure which interferes with the arterial supply **[34-39]**.

- **Nerve root compression:** Compromise of the nerve roots may develop following disc protrusion or osteophytosis **[40]**. Spinal nerve roots are exquisitely sensitive to compression **[41-43]**.

- **Local irritation:** This includes irritation of mechanoreceptive and nociceptive fibers within the intervertebral motion segments **[44]**.

- **Vertebral artery compromise:** MacNab advises that osteophytes may cause vertebral artery compression **[45]**.

- **Autonomic dysfunction:** Symptoms associated with the autonomic nervous system have been reported in patients with cervical spine trauma. The Barre’-Lieou syndrome includes blurred vision, tinnitus, vertigo, temporary deafness, and shoulder pain. This phenomenon is also known as the posterior cervical syndrome **[46]** Stimulation of sympathetic nerves has been implicated in the pathogenesis of this syndrome **[47]**.

- **Coherence and oscillatory patterns:** Coherent oscillations are a characteristic of the human brain. **[48]** Furthermore, it has been proposed that synchronization of multiple rhythms is an essential manifestation of living processes **[49]**. Epstein describes wave activity association with Network Spinal care, a chiropractic technique involving light touches to the spine. According to Senzon, Epstein and Lemberger, “The network wave occurs at a higher self-organizational threshold, in the absence of significant adverse mechanical cord tension, and with enhanced self-regulation of the spinal subsystems. With

the onset of central pattern generation, modulated through the network wave, reorganizational behavior may emerge in the individual's spine and life as a whole" **[50]**.

6.2. Operational Model of Vertebral Subluxation

The author has proposed an operational model for the assessment of neurological dysregulation associated with vertebral subluxation **[51]**. The four components of this model include:

- **Dysafferentation:** The intervertebral motion segment is richly endowed with nociceptive and mechanoreceptive structures **[52-57]**. As a consequence, biomechanical dysfunction caused by vertebral subluxation may result in altered nociception and/ or mechanoreception.

- **Dyskinesia:** Dyskinesia refers to distortion or impairment of voluntary movement **[58]**. Spinal motion may be reliably measured using inclinometry **[59]**. Alterations in regional ranges of motion may be associated with vertebral subluxation **[60]**.

- **Dysponesis:** Dysponesis is evidenced by abnormal tonic muscle activity. Dysponesis refers to a reversible physiopathologic state consisting of errors in energy expenditure, which is capable of producing functional disorders. Dysponesis consists mainly of covert errors in action potential output from the motor and premotor areas of the cortex and the consequences of that output. These neurophysiological reactions may result from responses to environmental events, bodily sensations, and emotions. The resulting aberrant muscle activity may be evaluated using surface electrode techniques **[61,62]**. Typically, static surface electromyography (sEMG) with axial loading of the spine is used to evaluate innate responses to gravitational stress **[63]**.

- **Dysautonomia:** The autonomic nervous system regulates the actions of organs, glands, and blood vessels. Acquired dysautonomia may be associated with a broad array of functional abnormalities **[64-70]**. Sympathetic tone may be evaluated by measuring skin temperature differentials using paraspinal infrared thermography **[71]**. Such techniques have been used to monitor changes in neurological function associated with vertebral subluxations **[72]**.

7. Autonomic Dysregulation and Mental Health

Variability in heart rate reflects the vagal and sympathetic function of the autonomic nervous system, and is used as a monitoring tool in clinical conditions characterized by altered autonomic nervous system activity. Spectral analysis of beat-to-beat variability is a simple, non-invasive technique to evaluate autonomic dysfunction. Vertebral subluxations are changes in the position or motion of a vertebra, which result in the interference with nerve function. Vertebral subluxations may result in altered autonomic nervous system activity. Heart rate variability is a reliable and valid tool that may be used to assess the changes in autonomic activity associated with the reduction and correction of vertebral subluxations **[72]**. Recent studies have reported the potential utility of HRV in the evaluation of conditions and states associated with autonomic dysregulation. These include carotid intima media thickness **[73]**, prediction of mortality **[74]**, multiple sclerosis **[75,76]**, eating behavior **[77]**, burnout and depression **[78]**, chronic posttraumatic stress disorder **[79]**, working memory performance **[80]**, dementia **[81]**, inflammation in rheumatoid arthritis **[82]**, insulin resistance and metabolic syndrome **[83]**, type 1 diabetes **[84]**, cardiac autonomic nerve function in obese school-age children **[85]**, cancer prognosis **[86,87]** and cognition **[88,89]**. In the mental health field, associations have been identified between cardiac vagal activity, immunometabolic risk factors, and depression **[90].** Higher Beck Depression Inventory-II (BDI-II) scores were associated with decreased HRV **[91]**. Oh and Chae **[92]** note that HRV may be a crucial marker for mental health. They report that "HRV properties might be related to the degree of optimistic perspectives on life, and suggests that HRV markers of autonomic nervous system function could reflect positive human mind states." Fiskum et al **[93]** state, "Internal psychopathology and dysregulated negative affect are characterized by dysregulation in the autonomic nervous system and reduced heart rate variability (HRV) due to increases in sympathetic activity alongside reduced vagal tone…Higher informational entropy was related to less psychopathology and less

negative effect, and may provide an index of the organizational flexibility of the neurovisceral system."

Polyvagal theory (PVT), proposed by Porges **[94]** posits that physiological state limits the range of behavior and psychological experience. Porges notes, "The theory links the evolution of the autonomic nervous system to affective experience, emotional expression, facial gestures, vocal communication, and contingent social behavior. In this way, the theory provides a plausible explanation for the reported covariation between atypical autonomic regulation (eg, reduced vagal and increased sympathetic influences to the heart) and psychiatric and behavioral disorders that involve difficulties in regulating appropriate social, emotional, and communication behaviors." Sullivan et al **[95]** explain that "PVT links the evolution of the autonomic nervous system to the emergence of prosocial behaviors and posits that the neural platforms supporting social behavior are involved in maintaining health, growth and restoration. This explanatory model which connects neurophysiological patterns of autonomic regulation and expression of emotional and social behavior, is increasingly utilized as a framework for understanding human behavior, stress and illness." The authors describe how PVT is related to self-regulation, resilience, and adaptability. Smith et al **[96]** proposed the neurovisceral integration (NVI) model to explain observed relationships between peripheral physiology, cognitive performance, and emotional and physical health. This model is supported largely from studies examining cardiac vagal control. An expanded model describes the multilevel structure and function of vagal control. Higher levels are associated with cognitive/attentional responses, regulation based on perceptual representation of one's current somatic/visceral state, regulation based on conceptualization of sensory input and past experience, and amplifying, maintaining, or suppressing representations based on current goals. In reviewing the literature concerning HRV and chiropractic care, Kent concluded, "Case reports suggest that favorable changes in heart rate variability may follow reduction or correction of vertebral subluxations. Higher quality studies of larger populations should be conducted. It is biologically plausible that the changes in autonomic nervous system function following reduction or correction of vertebral subluxation may be objectively assessed using heart rate variability" **[72].**

8. Conclusion

Chiropractic care is concerned with the totality of the human experience. Vertebral subluxations may result in autonomic dysregulation, compromising the adaptive capacity of the organism. By analyzing and correcting vertebral subluxations, a patient is placed on a more optimum physiological path, potentially increasing resilience and adaptability. Further research into the effects of vertebral subluxations on mental health, the neurobiological mechanisms involved, and the use of reliable and valid outcomes assessments should be undertaken. It is biologically plausible that vertebral subluxations compromise nervous system function and affect mental health.

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