



NEURODEGENERATIVE AND NEUROINFLAMMATORY DISARRAYS IN PROGENIES AND ADULTS

**MOHANAPRIYA CHELLADURAI*, SANGEETHA DAMODARAN, RENGARAJ SAHASRANAM,
VAISHNAVI DEVI SRINIVASAN, KARTHIKEYAN VIJAYAN AND GOPINATH MARGAVELU.**

*Department of Biotechnology, KarpagaVinayaga College of Engineering and Technology,
Madurantakam, Kanchipuram Dt, Tamil nadu, India.*

ABSTRACT

Neurodegenerative disorders of childhood encompass a large, heterogeneous group of diseases that result from specific genetic and biochemical defects, chronic viral infections, and varied unknown causes. Progenies with suspected neurodegenerative disorders were once subjected to brain and neural biopsies, but with modern neuroimaging techniques and specific biochemical and molecular diagnostic tests, these invasive procedures are rarely necessary. The hallmark of a neurodegenerative disease is regression and progressive deterioration of neurologic function with loss of speech, vision, hearing, or locomotion, often associated with seizures, feeding difficulties, and impairment of intellect. Neuroinflammation is yet another neuronal disorder which is the inflammatory responses in acute damages and disorders necessary for homeostatic and defensive mechanisms of repair, regeneration and healing, chronic inflammatory signals in low-grade magnitude promote the development of a host of disorders ranging from cancer, diabetes, hypertension and cardiovascular disorders (CVDs). In total, the current review focuses our knowledge in the field of factors influencing inflammation and the mechanisms of metabolic dysfunctions. Also, anti-inflammatory therapies for chronic diseases have been successful to some extent. The effects of metabolic inflammation due to chronic factors is not just circumscribed to the peripheral metabolic tissues as was believed earlier, but is etiologically important for the CNS and especially the hypothalamus which drives central dysregulation of metabolic homeostasis.

KEYWORDS: Neurodegenerative diseases, Neuroinflammation, progenies, adults, treatment.



*Corresponding author

MOHANAPRIYA CHELLADURAI

Department of Biotechnology, KarpagaVinayaga College of Engineering and
Technology, Madurantakam, KanchipuramDt, Tamil nadu, India.

INTRODUCTION

Neurodegeneration refers to several conditions that result in progressive loss of neuronal structure, function and neuronal death. Some of the better known neurodegenerative disorders include Parkinson's disease, Alzheimer's disease and Huntington's disease. Neurodegenerative disease is rare in progenies. The approach relies on a high index of suspicion and the collation of all relevant clinical data so that the correct investigations are made. Making a correct diagnosis holds significance for genetic counseling and hopefully, the prevention of diseases¹.

Neurodegenerative Diseases

All of these conditions lead to progressive brain damage and neurodegeneration. Although all three of the diseases manifest with different clinical features, the disease processes at the cellular level appear to be similar. Neurodegeneration may be identified at the molecular level and at the systemic or more generalized level. With age, the risk of DNA mutation increases, as well as the risk of cell damage induced by oxidative stress. These factors increase the risk of developing neurodegenerative disorders². Neurodegenerative diseases are usually characterized by onset in late adulthood, a slowly progressive clinical course and neuronal loss with regional specificity in the central nervous system. In Alzheimer disease, Parkinson disease (PD), spinocerebellar ataxias and amyotrophic lateral sclerosis, neurodegeneration preferentially involves the cerebral cortex, extrapyramidal system, cerebellum and spinal cord, respectively. Although the majority of neurodegenerative diseases are sporadic, Mendelian inheritance patterns have been well documented. Intriguingly, the clinical presentations and neuropathological findings of hereditary forms of these neurodegenerative diseases are often indistinguishable from the sporadic diseases, raising the possibility that common pathophysiologic mechanisms underlie both hereditary and sporadic neurodegenerative diseases³.

Neurodegenerative diseases in progenies

The detection of neurodegenerative and neurometabolic diseases in children relies on a high index of suspicion as most will present as common paediatric problems such as recurrent vomiting, feeding problem, failure to thrive, sepsis, or developmental delay. Alternatively, children may present with an acute encephalopathy or with a chronic progressive encephalopathy⁴. Clinical clues suggestive of neurometabolic disorders include encephalopathic features such as microcephaly, macrocephaly, developmental regression, developmental arrest, change in sensorium, seizures, hypotonia, hypertonia, abnormal eye signs; also extrapyramidal or cerebellar signs and systemic features like abnormal respiration, hepatosplenomegaly, abnormal hair, liver dysfunction, renal tubular dysfunction, cardiomyopathy, and feeding difficulties or growth problems. Initial screening includes tests for acidosis, ketosis, hyperlactemia, and hyperammonemia. Further investigations should include amino acid chromatography, assays of organic acids, specific enzyme assay of white cell or fibroblast culture, and histopathology of cell and tissue biopsy (white blood cell, skin, muscle, conjunctiva, bone marrow, liver, rectum, or brain). The correct diagnosis holds implications for targeted therapeutic intervention, genetic counselling, and prenatal diagnosis⁵.

Clinical features of Neurodegenerative diseases in progenies

If the grey matter is affected, the child presents with abnormalities of cognition (mental retardation), vision, hearing, and seizures. If the white matter is affected, there may be loss of motor skills, spasticity, or ataxia. These distinguishing features are useful only in the early stages of the disease, as both grey and white matters are involved at a later stage as the disease progresses⁶.

Fraught in neurodegenerative diseases

The detection of ND is often hampered by the failure to recognize that which usually presents as a common paediatric problem (sepsis, recurrent vomiting, feeding problem,

failure to thrive, intrauterine growth retardation, developmental delay). In addition, children may present with unexplained mental retardation, cerebral palsy, or epilepsy. A well taken history is an essential prerequisite to a thorough investigation. The child neurologist when faced a child with a progressive encephalopathic picture, has to decide if the involvement is restricted to the central nervous system solely or if there is multisystem involvement; whether the disease is limited to the central nervous system only, or the peripheral nerves; and whether there is grey matter or white matter involvement⁷.

Features of Neurodegenerative diseases

The presenting features of children with neurodegenerative can be acute, fulminating, and rapidly progressive, or subtle and slowly progressive. A time course and sequential neurological and developmental assessments are needed to distinguish a static encephalopathy from a slowly progressive degenerative disease. Of course, treatable conditions such as space-occupying lesions, infections, and metabolic disorders need to be excluded⁸.

Categories of Neurodegenerative diseases

Neurodegenerative diseases that present with acute encephalopathy include maple syrup urine disease, organic acidurias, lactic acidosis, urea cycle disorders, and non-ketotichyperglycinemia. Routine studies include the determination of blood gas, ketones, lactate, and ammonia and special studies such as urine analysis for the presence of organic acids and amino acids⁹. Neurodegenerative disease that appears as a chronic progressive encephalopathy includes sphingolipidosis, mucopolysaccharidosis, glycoprotein degradation disorders, peroxisomal disorders, fatty acid oxidation disorders, and neuronal ceroidlipofuscinosis. Routine studies include urine analysis for mucopolysaccharides and oligosaccharides. Special studies include looking for inclusion bodies in lymphocytes, very long chain fatty acids, and lysosomal enzymes. The definitive diagnosis for both categories rests on enzyme assay in white blood cells, skin fibroblasts, and tissue¹⁰.

Neurodegenerative disease on metabolic bases

The clinical features that suggest Neurodegenerative diseases with a metabolic cause are mainly neurological and systemic ones. Neurological features include frequent epileptic seizures (especially infantile spasm, myoclonus), a gradual development of spasticity, dementia, developmental regression, visual or auditory deterioration, extrapyramidal symptoms, cerebellar symptoms, microcephaly, macrocephaly, speech problems, or psychiatric symptoms. Abnormal eye examination includes optic atrophy, retinal depigmentation, abnormal eye movement, oculomotor dyspraxia, nystagmus, tapetoretinal degeneration, and cherry red spots. Suggestive systemic features include intrauterine growth retardation, failure to thrive, poor sucking, weak cry, repeated vomiting, and susceptibility to infection, seborrhea, alopecia, abnormal hair, abnormal urine odour, renal tubular degeneration, bone marrow depression, cardiomyopathy, hepatomegaly, hepatosplenomegaly, or typical features of gargoylism. The pathogenesis of ND is related to the synthesis, metabolism, transport, and storage of biochemical compounds. Among the 300 inborn errors of metabolism, the central nervous system is involved in about one third of cases. This includes organic acidurias, aminoaciduria, lysosomal storage disorders (sphingolipidosis, mucopolysaccharidoses, glycoprotein degradation disorders), fatty acid oxidation disorders, congenital lactic acidosis, peroxisomal disorders, urea cycle disorders, and neuronal ceroid lipofuscinosis⁶. Neurometabolic disorders can present either with acute encephalopathy or as chronic progressive encephalopathy. With the former, the age of onset is usually in the neonatal or early infancy period, with predominantly grey matter involvement. The clinical features include cognitive impairment, seizures, visual impairment, vomiting, lethargy, coma, and abnormal respirations. With chronic progressive encephalopathy, the onset is usually in infancy, childhood, or adolescence, with predominantly white matter involvement. Features include spasticity, ataxia, hyperreflexia, liver dysfunction, cardiomyopathy and weakness⁷. Metabolism

is controlled by a complex system of transcriptional events and posttranslational modifications stimulated by substrate and metabolite availability. It is becoming clear that neurodegenerative diseases are a symptom of a deficiency in the regulation or execution of metabolic reactions. Mitochondria, as the central organelles in metabolic regulation as well as the chief generators of reactive species, clearly have a role to play in the etiology of neurodegenerative conditions⁹.

Consequence of Hysterectomy and oophorectomy in Neurodegenerative diseases

The long-term cognitive effects of hysterectomy and oophorectomy remain controversial. Some studies indicate that hysterectomy and oophorectomy may have harmful brain effects via direct endocrinological mechanisms, and estrogen deficiency appears to play a key role in these associations. Other studies indicate that use of hormone replacement therapy subsequent to hysterectomy may increase the risk of neurodegenerative diseases such as Parkinson's disease. The subject is poorly investigated and there is no consensus on the possible cognitive effects of hysterectomy¹⁰.

Effect of intracellular protein aggregates in Neurodegenerative diseases

The formation of intracellular aggregates is a common etiology of several neurodegenerative diseases. Mitochondrial defects and oxidative stress have been pointed as the major mechanistic links between the accumulation of intracellular aggregates and cell death. A "metabolic cell death by overcrowding" as an alternative hypothesis. Using a model of neuron metabolism, we predict that as the concentration of protein aggregates increases the neurons transit through three different metabolic phases. The first phase (0–6 mM) corresponds with the normal neuron state, where the neuronal activity is sustained by the oxidative phosphorylation of lactate. The second phase (6–8.6 mM) is characterized by a mixed utilization of lactate and glucose as energy substrates and a switch from ammonia uptake to ammonia

release by neurons. In the third phase (8.6–9.3 mM) neurons are predicted to support their energy demands from glycolysis and an alternative pathway for energy generation, involving reactions from serine synthesis, one carbon metabolism and the glycine cleavage system. The model also predicts a decrease in the maximum neuronal capacity for energy generation with increasing the concentration of protein aggregates. Ultimately this maximum capacity becomes zero when the protein aggregates reach a concentration of about 9.3 mM, predicting the cessation of neuronal activity¹¹.

Symptoms of Neurodegenerative diseases

Degenerative nerve diseases affect many of your body's activities, such as balance, movement, talking, breathing, and heart function. Many of these diseases are genetic. Sometimes the cause is a medical condition such as alcoholism, a tumor, or a stroke. Other causes may include toxins, chemicals, and viruses. Sometimes the cause is not known. Degenerative nerve diseases can be serious or life-threatening. It depends on the type. Most of them have no cure. Treatments may help improve symptoms, relieve pain, and increase mobility¹².

Intoxications and energy deficiencies in Neurodegenerative diseases

Intoxications results from accumulation of toxic metabolites proximal to the blockage of metabolic pathway. This includes organic acidurias, amino acidurias, urea cycle defects, galactosemia, fructosemia, and tyrosinemia. Energy deficiencies are caused by the impaired production or use of energy due to defects in the liver, myocardium, muscle, or brain. This includes glycogen storage disorders, congenital lactic acidosis, fatty acids oxidation defects, mitochondrial disorders, and peroxisomal disorders¹².

Types of onset in Neurodegenerative diseases

Brain iron increases with age and is abnormally elevated early in the disease process in several neurodegenerative disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD). Higher iron levels in males may contribute to higher risk for younger-onset PD and recent studies

have linked the presence of the hemochromatosis gene with a younger age at onset of AD. There can be various ages of onset of the illness. This can be neonatal (less than one month), early infantile (1-12 months), late infantile (1-4 years), and late childhood (juvenile, 5-15 years). Some diseases can present at different ages with differing degrees of severity. The age of onset is important for deciding the clinical approach to various categories of ND¹³.

Neonatal

The neurodegenerative disorders of childhood are a diverse group of rare disease that until recently were a death sentence of the most horrible kind. These diseases can result from genetic problems, biochemical defects, viral infections, or toxic substances. The hallmark of this disease is a progressive loss of speech, hearing, vision, and strength. Seizures, feeding difficulties, and loss of intellect often accompany with this downhill course. Diseases with onset at birth include generalised GM₁ type I gangliosidosis, type I glycogen storage disease, neonatal adrenoleukodystrophy, mucopolipidosis II, and Alexander's disease¹⁴.

Early infantile

Disorders with onset at one to three weeks include galactosemia and maple syrup urine disease. Onset at one to three months includes type II glycogen storage disease (Pompe's) and the infantile type of neuronal ceroidlipofuscinosis. Disease with later onset at three to six months include Gaucher's disease. Tay-Sachs disease, Krabbe's disease, Niemann-Pick disease; those with onset at three to twelve months include the Lesch-Nyhan syndrome and PelizaeusMerzbacher disease¹⁵.

Late infantile

Diseases with onset at six months to two include adrenoleukodystrophy and juvenile GM₁ gangliosidosis type II; onset at six months to four years includes Hurler's syndrome, metachromatic leukodystrophy, neuroaxonal dystrophy, and Leigh's disease. Onset at one to six years includes type C Niemann-Pick disease, whereas later onset (at 2-5 years) includes the late infantile type of neuronal ceroidlipofuscinosis. Onset at two

to six years includes Hunter's syndrome and GM₂ type III gangliosidosis¹⁶.

Late childhood

Disease onset at four to eight years includes the juvenile form of neuronal ceroidlipofuscinosis and Sanfilippo syndrome; at five to ten years it includes adrenoleukodystrophy and Huntington's chorea. Onset at eight to 15 years includes juvenile metachromatic leukodystrophy, Gaucher's disease type III (juvenile form), mucopolipidosis I, and Hallervorden-Spatz syndrome¹⁷.

Maiden and unconventional diagnosis in Neurodegenerative diseases

General initial laboratory studies include blood analysis for the following: complete blood count, glucose, calcium, anion gap, electrolytes, ammonia, aminotransferases, lactic acid, pyruvic acid, uric acid, ketones (β-hydroxy-butyric acid and acetoacetic acid). Urine analysis is performed for odour, pH, ketones, and to screen for metabolites. Positive urine screening for metabolic disorders includes: dinitrophenylhydrazine (phenylketonuria or other aminoaciduria), ferric chloride and dinitrophenylhydrazine (organic aciduria), reducing substance (galactosemia), nitroprusside (homocystinuria), and cetyltrimethylammonium bromide or Berry spot (mucopolysaccharidosis)¹⁸.

Preliminary investigations include looking for vacuolation of the lymphocytes (gangliosidosis, glycoprotein degradation disorders), raised acid phosphatase (Gaucher's disease), and metachromatic granules in the urine (metachromatic leukodystrophy). Raised serum lactate occurs in mitochondrial disorders and in Alpers' disease. Hyperammonemia occurs with some NDs such as carbamyl phosphate synthetase deficiency, ornithine transcarbamylase deficiency, or organic aciduria¹⁸.

Supplementary investigations

Lactate and pyruvate levels are raised in mitochondrial disorders and the protein level is raised in leukodystrophy and other demyelinating disorders. Children with dysmorphic features need chromosomal

studies. Chromosomal analysis has been found to be associated with certain disorders-chromosomes 1 and 16 in neuronal ceroidlipofuscinosis and chromosome 21 in progressive myoclonus epilepsy (Lafora disease)¹⁹.

Electroencephalogram

With diffuse cortical and subcortical grey matter disease there are bilaterally synchronous paroxysmal discharges. In white matter disease, the electroencephalogram (EEG) may show continuous non-paroxysmal slow wave activity. In infantile neuronal ceroidlipofuscinosis, there is a progressive reduction in amplitude after infancy, and high voltage complexes are induced posteriorly with a slow rate of photic stimulation. In infantile neuroaxonal dystrophy, diffuse fast (beta) waves of moderate amplitude develop after two years of age. In progressive neuronal degeneration of childhood (Alpers' disease), multiple spikes superimposed on lateralized large slow waves are found, and this predicts later liver involvement¹⁹.

Electroretinogram

The electroretinogram (ERG) provides information about the retina by averaging the response to repeated light flashes, both the photopic and scotopic (dark-adapted) response. Low or extinguished ERGs are found in those with congenital low vision (peroxisomopathies) and late onset of low vision (neuronal ceroidlipofuscinosis, mitochondrial cytopathy, Refsum's disease, Hunter's syndrome, and mucopolipidosis type IV)¹⁹.

Visual evoked potential

In children, it is useful to record the ERG, visual evoked potential (VEP), and EEG to document the site and type of lesion. In disorders of the peripheral retina (e.g. early stage of retinitis pigmentosa), the ERG may be absent but the VEP may be normal. If there is diffuse involvement of the retina, including the macula and the periphery, both the ERG and VEP will be absent. If only the retinal ganglion cells degenerate (e.g. infantile GM₂ gangliosidosis), the ERG is normal and the VEP may be absent. Diagnostic test evaluating specific tracts of the central and peripheral nervous

system. May include visual, auditory, or somatosensory evoked potentials. These record the electrical responses of the brain and spinal cord to the stimulation of the senses¹⁹.

Brainstem auditory evoked potential

This assesses the integrity of the auditory nerve (sensorineural deafness) and the central auditory pathway (brainstem). Increased interpeak latency of waves I-V may be found in a demyelinating disorder and a reduction of wave V amplitude (i.e. decreased wave V: wave I ratio) may be found in an axonal lesion¹⁹.

Nerve conduction study

Motor and sensory nerve conduction study differentiates between demyelinating and axonal neuropathies. The nerve conduction velocity is markedly decreased in demyelinating neuropathy and the amplitude of the motor or sensory action potential is decreased in axonal neuropathy¹⁹.

Electromyogram

This is useful for differentiating denervation/neurogenic changes from myopathic changes. Abnormal spontaneous activity (e.g. fibrillations) are found in denervation but also in some myopathies. Abnormality on exertional activity is more useful for differentiating the lesions. In neurogenic lesion, the interference pattern is reduced, whereas the duration of the motor unit potential is long and the amplitude is high. In myopathy, the interference pattern is full and the motor unit potential is of short duration and low amplitude¹⁹.

Radiology in Neurodegenerative diseases

Specific skeletal changes are found in mucopolysaccharidosis, mucopolipidosis, gangliosidosis, and homocystinuria. A computed tomography (CT) scan of the brain will show any intracranial calcification and non-specific changes of cortical atrophy. White matter hypodensities can be found in leukodystrophies, aminoacidopathies (maple syrup urine disease, phenylketonuria), and in peroxisomopathy (Zellweger syndrome). Striatal hypodensities are found in Leigh's disease, mitochondrial disorders, and in organic aciduria (methylmalonicaciduria). A

magnetic resonance image (MRI) scan of the brain is more sensitive than a CT scan in defining the extent of lesions in demyelinating and dysmyelinating disorders. The sensitivity of an MRI scan in detecting these disorders is equal to a CT scan. Single photon emission computed tomography (SPEC) provides information on the cerebral blood flow in stroke, which can help to differentiate vascular from metabolic stroke in mitochondrial encephalopathy lactic acidosis and stroke. In contrast, the positron emission tomography (PET) scan provides information on the metabolism of the brain¹⁹.

Cell and tissue level diagnosis in Neurodegenerative diseases

An enzyme assay of leukocytes or cultured skin fibroblast can assist in making a definitive diagnosis. Cells and tissues can also help in making the diagnosis in some disorders. Vacuolated lymphocytes are found in mucopolysaccharidosis (very numerous and small), the juvenile type of neuronal ceroidlipofuscinosis (NCL) [few but larger], and in other lysosomal storage diseases (infantile type of GM₁gangliosidosis, Niemann-Pick disease type A, mannosidosis, fucosidosis). Examination of the buffy coat under electronmicroscopy is useful in making a diagnosis of neuronal ceroidlipofuscinosis. Membrane-bound granular osmophilic deposits are found in many lymphocytes in late infantile NCL. In infantile NCL, autofluorescence is detected under ultraviolet light. In metachromatic leukodystrophy, toluidine blue staining of urine sediment can show the golden-yellow metachromatic material in renal epithelial cells and green birefringence of the renal epithelial cells are found in polarized light. In infantile neuronal ceroidlipofuscinosis, yellow autofluorescence is found with ultraviolet light. Twisted hair (pili torti) is found in Menkes' disease and arginosuccinicaciduria. Intermittent swollen breaks (trichorrhexis nodosa) may be found in Menkes' disease, biotinidase deficiency, and arginosuccinicaciduria. The conjunctiva is rich in nerve fibres. Curvilinear bodies are found in NCL. In mucopolysaccharidosis type IV, multilaminar bodies may be seen in epithelial and endothelial cells. In neuroaxonal dystrophy, dystrophic axons with

spheroids may be found in the conjunctiva and skin. The muscle in some mitochondrial encephalopathies shows the typical ragged red fibres with Gomori trichrome stain. Abnormalities of the succinic dehydrogenase reaction may suggest mitochondrial disease, even in the absence of ragged red fibres.⁹ The muscle fibres contain Periodic Acid Schiff and peroxidase positive granules in Lafora body disease. In neuroaxonal dystrophy, the spheroids may be found in the intramuscular nerve. Biochemical study of the electron transport chain in mitochondrial disorders can be performed. Biopsy of the peripheral nerves shows neuroaxonal spheroids in infantile neuroaxonal dystrophy. A brain biopsy may help in the diagnosis of demyelinating diseases (Alexander disease and Canavan's disease). In neuroaxonal dystrophy, brain biopsy with esterase histochemistry may provide a definitive diagnosis in those with negative findings in skin, conjunctiva, or muscle biopsies. In NCL, autofluorescence under ultraviolet light and electron microscopic findings provide a definitive diagnosis if other tissue examinations have been unrevealing. In peroxisomopathies, the liver biopsy may show a decrease in peroxisome numbers or enlarged peroxisomes with abnormal shapes.¹⁰ In progressive neuronal degeneration of childhood (Alpers' disease), fatty infiltration or cirrhosis may be found. Bone marrow aspiration may show the typical cells found in Gaucher's disease and Niemann-Pick disease²⁰.

Prevailing and progressive treatments

Treatment of most NDs or neurometabolic diseases is mainly supportive. Dietary restriction is useful in certain diseases (phenylketonuria, maple syrup urine disease, enocephalopathy), and prenatal diagnosis is possible in some diseases. An assay of enzyme in cells can be obtained by chorionic villus sampling (8-12 weeks gestation) or amniotic fluid (14-16 weeks gestation). Bone marrow transplantation has been tried with various diseases, and has shown promising results when performed at a stage where irreparable brain damage has not occurred. This includes lysosomal storage diseases, mucopolysaccharidosis. Gaucher's disease, metachromatic leukodystrophy, and

adrenoleukodystrophy. Somatic gene therapy targeted at the central nervous system is still at the embryonic stage. Neuronal transplants using foetal brain tissue have been conducted, but immunological and ethical issues are matters of concern. Due to limitations posed by the restrictive blood-brain barrier, conventional drug delivery systems do not provide adequate cyto-architecture restoration and connection patterns that are essential for functional recovery in neurodegenerative disorders (NDs). Nanotechnology employs engineered materials or devices that interact with biological systems at a molecular level and could revolutionize the treatment of NDs by stimulating, responding to, and interacting with target sites to induce physiological responses while minimizing side effects²⁰.

Antibody as therapeutic agents in Neurodegenerative diseases

Developing therapies for neurodegenerative disease is of the high priority due to the enormous cost of medical care required, as well for the human suffering involved. Although caused by the variety of genetic and environmental insults, such diseases causes commonalities. Many of these diseases are proteinopathies – diseases caused by misfolded, aggregating proteins. Antibodies that can recognize and remove misfolded proteins are ideally suited for proteinopathy therapeutics²⁰.

Stem cells as therapeutic agents in Neurodegenerative diseases

Stem cells offer an enormous pool of resources for the understanding of the human body. One proposed use of stem cells has been as an autologous therapy. The use of stem cells for neurodegenerative diseases has become of interest. Clinical applications of stem cells for Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, and multiple sclerosis will increase in the coming years, and although great care will need to be taken when moving forward with prospective treatments, the application of stem cells is highly promising²⁰. Neurodegenerative diseases hold an opportunity for the clinical use of stem cells. In neuroscience, the discovery of neural stem cells (NSCs) and subsequent research have nullified the previous

idea that the adult CNS was not capable of neurogenesis. Indeed, neurogenesis occurs throughout life. NSCs are believed to reside within the subventricular zone of the lateral ventricle wall and the subgranular zone of the hippocampal dentate gyrus, where neurogenesis occurs¹⁴⁻¹⁵. NSCs give rise to glial-restricted precursors (GRPs) and neuron-restricted precursors, both of which differentiate into astrocytes, oligodendrocytes, or neurons. Another study demonstrated that transplanted NSCs isolated from a 9-week-old human fetus have the ability to differentiate into neural cells and improve cognition in aged rats. Hence, the idea of using NSCs for neurodegeneration treatment is intriguing²⁰. However, NSCs are not so easy to access as a source of stem cells for possible use to treat neurodegenerative diseases. Previously, many studies have suggested the use of bone marrow-derived mesenchymal stem cells (MSCs) for regeneration of neural cells since MSCs are present in bone marrow and are relatively easily accessible within the human body. However, the consensus now is that naive MSCs do not become neural cells. Our previous study suggests that MSCs can be dedifferentiated into cells similar to iPS cells by increasing the expression of a single ESC gene. We were able to transdifferentiate MSCs into neural cell lineage after dedifferentiation. This result indicates that we may be able to use adult stem cells as an autologous source to create iPS cells. This technology and iPS cells together may offer the potential for autologous neuroregenerative therapies to be developed along with the ease of access to a patient's own cells. Another key factor for the development of stem cell treatments for neurological diseases will be the understanding of the pathology of the specific disease. Each disease will need to be assessed individually and each treatment will need to be tailored accordingly²¹.

Neuroinflammation

Inflammation of the central nervous system (CNS) is characterized by increased glial activation, pro-inflammatory cytokine concentration, blood-brain-barrier permeability, and leukocyte invasion. One key player that is believed to drive this neuroinflammatory process is interleukin (IL)-1 beta, a pro-inflammatory cytokine that is up-regulated in Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis, and other neurodegenerative disorders. IL-1 beta signals through the type I IL-1 receptor/IL-1 accessory protein complex, leading to NFkB-

dependent transcription of pro-inflammatory cytokines (tumor necrosis factor (TNF)-alpha, IL-6, and interferons) and neutrophil-recruiting chemokines (CXCL1 and CXCL2) in glia²². The etiologies of such chronic inflammatory factors are varied: in some cases, genetic inflammatory components work as a risk of developing chronic inflammatory diseases, and on the other hand, environmental factors such as smoke, stress, endocrine-disrupting pollutants and overnutrition (caloric excess) have been implicated as prominent triggering factors in the development and propagation of inflammation-related diseases. Studies across the fields of immunology and endocrinology have established that caloric excess induces persistent inflammation in the circulation and peripheral metabolic tissues, disrupts metabolic homeostasis of the body, and thus contributes to a family of disorders including obesity, insulin resistance, glucose intolerance, hyperlipidemia and hypertension, collectively known as metabolic syndrome²².

Neuroinflammation in obesity

The central nervous system (CNS), in particular the hypothalamus, has been recognized to play a decisive regulatory role in maintaining metabolic homeostasis. Inflammation in the brain, which can be induced under chronic overnutrition, can disrupt neurohormone- and neurotransmitter-mediated central regulatory functions to propagate obesity and related disorders. Lately, neuroinflammation has been recognized to have an expansive contribution towards health problems and diseases. Recently, non-neuronal cell types like astroglia and microglia have been shown to act as additional platforms of inducing hypothalamic inflammation in diet-induced obesity thus broadening the scope of central inflammation-mediated metabolic dysfunctions²².

Neuroinflammation in diabetes

Overweight and obesity are major risk factors for many diseases such as hyperglycemia, T2D, hypertension, atherosclerosis, less high-density lipoprotein cholesterol levels, and hypertriglyceridemia, and historically, when patients have three or more of these symptoms with or without obesity, the

condition can be referred to as 'metabolic syndrome'. Recent studies indicate that excessive body weight and obesity can also be a facilitator and predictor of neurodegenerative diseases, thus possibly further enlarging the definition of 'metabolic syndrome'. Although pathogenic mechanisms encompassing this complex spectrum of disorders are yet to be fully understood, epidemiological, clinical and research studies have causally linked inflammatory factors and acute phase reactants such as C-reactive protein (CRP) TNF-alpha (TNF- α) IL-6 soluble adhesion molecules to metabolic disorders. Recent studies unveiled that some of the intracellular pathways of inflammation in the hypothalamus have causative roles in weight gain and related disorders. While the hypothalamus acts as the master regulator of energy balance by sensing metabolic cues and modulating the neurohormonal and neurotransmitter systems via endocrine signaling, trophic actions, complex neuronal plasticity and projections into the autonomic controlling centers of the brain inflammation in the hypothalamus can affect many, if not all, of these critical regulatory machineries to provide a neuropathological basis for the development of metabolic diseases²². In the event of metabolic inflammation, it seems that these first-order neurons get attacked readily, which negatively impact neuronal regulatory cascades such as leptin and insulin signaling, and also compromise the secretion of anorexigenic POMC-derived α -melanocyte stimulating hormone (α -MSH) and cocaine- and amphetamine-regulated transcript (CART), altogether resulting in increased appetite along with central leptin and insulin resistance to cause feeding and energy imbalance. Based on promising intervention results in animals, therapeutic strategies for human patients may expect to follow by targeting the key elements of inflammation in the neuronal and glial cells in order to counteract obesity and related comorbidities. The CNS can regulate whole-body glucose balance, and the hypothalamus governs the peripheral and central glucose homeostasis via multiple complex neural networks through neuropeptide and neurotransmitter actions. For example, central insulin and leptin signaling have been shown to be required for maintaining glucose homeostasis at least via suppressing hepatic glucose production and promoting peripheral glucose uptake²². From disease perspective, while literature over time has

convincingly established the role of overnutrition-induced weight gain and peripheral metabolic inflammation on development of glucose intolerance, insulin resistance, insulin insensitivity and leptin resistance. Recent findings revealed that systemic glucose homeostasis can be impaired by overnutrition-induced pathological activation of central immune system through body weight-independent mechanisms. Prolonged metabolic stress through overnutrition, in part through subjecting hypothalamic immune cells to a chronic state of overactivation, disrupts the normal physiological functioning of central insulin and leptin signaling that are needed for the control of systemic glucose homeostasis. For example, overnutrition-induced increases of intracellular stimuli, such as ligands of CRP, TNF- α , IL-6, TLRs, were all shown to activate IKK β /NF- κ B to cause insulin resistance and T2D. Also, intracellular stresses including reactive oxygen species (ROS) and ER stress are widely demonstrated to exert deleterious effects on glucose balance²³.

Effect of ROS in neuroinflammation

Regarding superoxides, we need to keep in mind that, while excessive production of ROS is classically associated with oxidative stress, pathology of insulin resistance, T2D, muscular dystrophies and aging, recent evidences showed that ROS can facilitate beneficial actions depending on the amount and source of its generation. Evidently, the beneficial or deleterious actions of ROS are determined by the source of its fuels and the amount of its accumulation at a given time in a particular cellular group. In this line, other studies have also reported that ROS, when generated within a boundary of low concentrations in the plasma membrane or the endomembrane can provide a protective action via normal cellular functioning and intracellular signaling which could be beneficial for reversal of insulin resistance. These findings give a new perspective of the protective actions of ROS which was classically believed to be an intra-cellular stressor. Recently, some epidemiological evidence interestingly demonstrated the lower mortality among mild overweight or small-degree (grade 1) obesity, while higher levels of obesity were associated with a significant risk of death, further highlighting the value of developing weight control-independent solutions for treating T2D and related deleterious complications²³.

Inflammasomes in diabetes and obesity

Also, inflammasomes, which are known as macromolecular innate immune cell sensors, have been recognized to increase metabolic stress, insulin resistance and obesity. Studies have also tackled Nod-like receptor 3 (NLRP3) inflammasome components, which can activate IKK β /NF- κ B pathway through inflammatory IL-1 β and IL-18 release. When NLRP3 was ablated in HFD-fed mice, it led to improved glucose tolerance and insulin sensitivity and prevented obesity-induced activation of adipose tissue interferon- γ expression. Collectively, these data suggested a potential role of inflammasomes in mediating IKK β /NF- κ B-dependent metabolic inflammation, and that molecular intervention in inflammasome-mediated pathways could improve obesity-associated inflammation and metabolic dangers²⁴.

Neuroinflammation in hypothalamus

Research during the past decades has focused on examining peripheral tissues relevant to the pathogenesis of obesity and related diseases, such as skeletal muscle, liver, and fat, because they represent the metabolic sites which are predominantly responsible for nutrient utilization and storage. One significant discovery is that many metabolic dysfunctions in peripheral tissues are causally related to local inflammation. Indeed, evidence derived from epidemiology, clinical medicine, and experimental research demonstrates that obesity and related diseases are associated with chronic low-grade inflammation in peripheral tissues and the circulation. Inflammation in several peripheral tissues is mounted by the immune system, as well as by non-immune cells, and is critically mediated by the proinflammatory IKK β /NF- κ B pathway. Recently, chronic overnutrition was shown to induce IKK β /NF- κ B-dependent inflammation in the CNS and particularly in the hypothalamus, a change that might contribute to the development of various over-nutrition-related diseases²⁴.

Neuroinflammation in hypertension

Hypertension is an integral component of obesity-related metabolic disorders and is a predictor of CVDs such as atherosclerosis

and stroke. While cardiac output, vascular compliance, blood volume and endocrine balance are major determinants of blood pressure, vasoconstriction and sodium retention are considered as primary contributors of hypertension and both processes are closely regulated by the CNS. Further studies recognized the contribution of inflammation in some of the peripheral components such as smooth muscles, endothelial cells and vascular macrophages towards the development of obesity-related hypertension. Although, the mechanism through which obesity directly induces hypertension is still an emerging area of investigation, an induction of neuroinflammatory condition has been observed in obesity-related hypertension. The convergent point of hypothalamic metabolic inflammation and SNS overactivation-mediated hypertension represents a novel platform for antihypertensive drug targeting. It is even more meaningful, since central NF- κ B pathway gains further support for anti-hypertensive drug targeting in general, in addition to obesity-related hypertension, as the inflammatory machinery has been found to be involved with several other forms of hypertension such as essential hypertension, spontaneous hypertension, and angiotensin II-induced hypertension, albeit the downstream mechanisms of NF- κ B could be different among these types of hypertension²⁴.

Neuroinflammation incardiovascular diseases

Uncontrolled high blood pressure is a predisposing risk factor of stroke. A growing number of recent investigations have established a critical role of brain inflammation in pathogenesis of ischemia and stroke in an obesity-dependent or obesity-independent manner. As a prophylactic or therapeutic option, several anti-inflammatory agents have been proven successful in treating stroke, and of interest, inhibition of brain IKK β /NF- κ B also provides a striking protection against ischemia²⁵.

Perceptions and Encounters

Although basic experimental research on animal models are the foundation of designing therapeutic strategies and drug

discovery, these models that are subjected to high fat/calorie feeding, intra-brain proinflammatory challenges or gene manipulations cannot unerringly clone the different pathological manifestations in patients across diverse race, feeding habits, behavioral practices and environmental cues. As a result, our biggest challenge remains in recapitulating the complex and sundry human disease conditions. While a 'top-down' approach could be attempting to replicate the disease symptoms and pathological causes, the reverse 'bottom-up' strategy of screening human populations for cellular and genetic alterations that mirror observed aberrations in experimental models will provide meaningful information²⁴. Another key aspect to be taken into account is the paradoxical actions of several classical toxic and degenerative elements in health and pathophysiological state. Overt concentrations of ROS contribute to inflammation-mediated metabolic deregulations, but subtle presence in confined regions convenes a protective action. Similar considerations need to be given to certain pro-inflammatory cytokines which have anorexic effects, as well as some cytokines which have anti-inflammatory actions. Of interest, slight weight gain has been shown to delay aging and mortality, which should increase our caution in order to develop appropriate anti-obesity strategies²⁵.

CONCLUSION

Neurodegeneration, the slow and progressive dysfunction and loss of neurons and axons in the central nervous system, is the primary pathological feature of acute and chronic neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease, neurotropic viral infections, stroke, paraneoplastic disorders, traumatic brain injury and multiple sclerosis. Despite different triggering events, a common feature is chronic immune activation, in particular of microglia, the resident macrophages of the central nervous system. Apart from the pathogenic role of immune responses, emerging evidence indicates that immune responses are also critical for neuroregeneration. Largely the challenge towards meaningful translation of basic

research findings to therapeutic options for patients remains in identifying the balance between the right environment, concentration and duration of the insults in experimental animal models. Regardless, chronic inflammation in the body, in particular in the CNS, represents a bold mechanistic player for a spectrum of metabolic syndrome-related diseases, and is clearly worth being a target for combating these human diseases. Convincing evidences from research during the past decade have established the contribution of neuroinflammation and in particular hypothalamic inflammation in the

pathogenesis of obesity, insulin resistance, T2D/pre-T2D and CVD. However, high risks to activate compensatory or counteracting mechanisms in some cases pose a challenge to strategize appropriate therapeutic options. Therefore, continuing research in understanding the detailed characteristics of neuroinflammatory mechanisms and neurodegeneration will be indispensable for harnessing the promising empiric findings to cogent therapeutic options, so that effective and selective therapies can be developed to treat patients without blunting other important aspects of health.

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