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Embryonic Cell Fate Predetermination in Neuronal and Ligodendrocyte Degeneration

Lawrence M. Agius
Department of Pathology, St Luke's Hospital,
Gwardamangia Medical School, University of Malta, Msida, Malta Europe

Abstract: Neuronal cell loss as preprogrammed pathways of cascade type might implicate such systems as oxidative stress in a setting of embryonic fate determination. Such programmed selectivity in neuronal susceptibility in diseases ranging from amyotrophic lateral sclerosis to Parkinson's disease and Alzheimer type dementia might integrally recategorize neurodegenerative states that evolve in terms of embryonic attributes of cell types and subtypes. Even multiple sclerosis as an apparent dichotomy of direct myelin damage and of an evolving pattern of oligodendrocyte loss might implicate systems such as cell lysis in terms of predetermined embryonic attributes of the oligodendrocyte that responds to injury. It is in terms of neuronal and glial participation of cell fate determination and response that one may account for a dual occurrence of familial and sporadic variants of disease entities that progress both as patterns of disease manifestation and as system progression of lesions in neurodegeneration or demyelination.

Key words: Cell fate, ligodendrocyte, neuronal

INTRODUCTION

Amyotrophic lateral sclerosis as dysfunctional consequences of oxidative stress: Amyotrophic Lateral Sclerosis (ALS) appears a consequence of oxidative stress insofar as it is possible to delineate dysfunctional effects of free oxygen radicals that injure membranes and protein-lipid moieties. The occurrence of inherited forms of ALS appears linked to mutants of cytochrome oxidase dismutase in a manner directly implicating oxidative stress in disease pathogenesis. Prenatal stress in experimental pregnant Wistar rats relates to apoptotic neurodegeneration in cerebellum and hippocampus[1].

Mitochondrinopathies are a source of oxidative stress apparently linked to neuronal ischemia-reperfusion and to myofiber necrosis distinct from evolving progression of ALS as a skeletal muscle atrophy of denervating type. Neuronal injury tends to promote oxidative stress that may be self-progressive. In terms of such self-progression, neuronal cell loss is a primary event beyond conventional disease pathogenesis but may constitute a core phenomenon of neurodegenerative disorders involving especially cell lysis or atrophy[2].

Neuronal cell loss may demarcate a series of events that analogously parallel apoptosis but that are primarily distinct both in terms of evolution and progression of the lesions. Dependence receptors initiate signal transduction by withdrawal of ligands and may result in caspase amplification and apoptosis in developmental cell death and neurodegeneration[3].

Is it possible to recognize an essential phenomenon of neuronal cell loss that is ultimately global, one that would involve selective vulnerability parameters but also primary and inherited attributes of embryonic development?[4]. Such a series of events arising from embryonic attributes may progress in much the same way that oxidative stress itself develops[5] but without the essential evolution of lesions induced by free oxygen radicals.

ALS may arise as an embyrologically derived disorder in which cell fate determination in neuronal cell loss progressively affects specific subsets of motor neurons.

Glia play a key role in removal of axon fragments during developmental axon pruning. Inhibition of axon pruning may result in synaptic degeneration and engulfment of degenerated axonal fragments by glia[6].

Cascade-type events may develop as a consequence of developmental biologic processes that involve cellular migration and cellular fate determination as processes that evolve in time and place and relative to cell size and sub-type. Selective neuronal vulnerability would implicate strict neuronal subtype as predetermined embryologically and developmentally. There is for example re-expression of the developmental protein nestin during neurodegenerative diseases in early stages of astroglial activation[7].

An anterior spinal horn targeting of neuronal cell loss would somehow be suggestive of modes of spinal muscular denervation that progress to involve adjacent

Corresponding Author: Lawrence M. Agius, 14, Guzeppi Caruana Street, Tal-virtu, Rabat, Malta Europe
Tel: +356 21451752 Fax: +356 21224286

muscle groups. ALS appears an integrative phenomenon involving skeletal muscle denervation and also a primary neuronopathy resulting in neuronal cell loss. During development, the survival of spinal motoneurons depends on the integrity of the connection to their peripheral targets[8]. Only in terms of such neuronal cell loss can one include modes of participation of selective vulnerability resulting in such cell loss. Skeletal myofiber denervation as a group myofiber phenomenon would necessarily constitute a heterogeneously distributed axonal lesion that progresses as such.

It seems important to draw a distinction between effective loss of neurons that is actively progressive and a phenomenon of neuronal evolution that is embyrologically acquired and that subsequently results in cell loss. Embryologically evolved cell loss is a process arising in the course of staged development of a lesion implicating cell loss independent of actual dynamics of onset of the injury.

Perinatal hypoxia/ischemia would directly trigger excitotoxic neurodegeneration, and apoptotic neurodegeneration would develop subsequent to a response of developing neurons to loss of development of normal synaptic connections[9].

Preselected loss of viability of neurons: Resolution of a process of neuronal cell loss might implicate the active prevention of events that in one way or another induce pre-determined loss of viability. A specific predilection for such events acting on subsets of neurons as aggregate events of progression would perhaps allow consequential evolution as neuronal cell loss. It is in determining how dementia or anterior spinal horn neurons are lost, or how substantia nigra neurons decrease in number, that one might better delineate schemes of influence in pathogenesis of disorders primarily labeled as neurodegenerative. Such schemes may incorporate toxic effects such as repeated ethanol administration that differentially affects caspase 3 and calpain activity and thus triggering apoptotic neurodegeneration[10].

Strict considerations of how neurons are lost both as individual cells and especially as aggregate subsets of specific neuronal type would perhaps allow better definition of a cell loss beyond simple biologic attributes of fertilization or of subsequent cell cycle division.

Age-related neurodegeneration may constitute a genetically programmed continuum of development and maturation, including oxidative stress as a defined hypothesis of aging[11].

A concept of such consequences of a fertilization event might in a real sense account for the progression, either of neuronal cell loss, or of primarily proliferative events. It is in the delineation of events of neuronal cell loss and of cell proliferation that one would better define pathogenic consequences as of primary significance. As a fertilization event with attributes of either cell division control or of actual cell proliferation, glial cells would also play an important role in the development of the normal and diseased adult brain[12].

Apoptosis, as a programmed cell death phenomenon, would prove a distinct process that derives from preprogrammed attributes of the fertilization event and of actual dynamics of cell division. Deregulation of transcription may contribute to the pathogenesis of neurodegeneration[13]. Cell loss is an embryologic determination not only arising as a consequence of developmental processes but particularly as active determinants of such development. Only in terms of how vulnerability is selective for certain neuronal subsets can one implicate pathways of cell loss preprogrammed to control excessive proliferative cell numbers. Indeed, it appears particularly significant that biologic systems of control have developed as control systems of cell proliferation and of cell number in primary evolution of the organism as a whole, as reflected in the autosomal recessive mutation wobbler of the mouse causing muscular atrophy due to motoneuron degeneration[14].

Dynamics of cell loss as integral expression of a disease process such as Alzheimer's that progresses in an age-related fashion, or of a disease such as Amyotrophic Lateral Sclerosis, would implicate attributes of oxidative stress injury to cortical neurons or to specific anterior horn neuronal subsets that are selectively programmed for cell loss rather than simply for the oxidative injury itself. On the other hand, enhanced apoptosis may not be apparent in the fetal Down syndrome brain or in the precocious neurodegeneration of the Alzheimer type[15].

A multiplicity of plaques in multiple sclerosis: Multiple Sclerosis (MS) constitutes events that self-resolve as plaques and progressively demyelinate in terms also of the resident oligodendrocyte pool.

And it is perhaps with reference to active demyelination as effective oligodendrocyte cell loss that multiple sclerosis would involve a multiplicity of insults that pathogenetically evolve and lead to oligodendrocyte cell loss. Demyelinative plaques are evolving oligodendrocyte cell loss that specifically implicate a degenerative event in the development of a disorder possibly also affecting axonal functionality. Multiple sclerosis may progress as relapses and remissions affecting the viability of oligodendrocyte populations of multiple plaques.

Oligodendrocyte fate determination would provide for the supply of myelin sheaths to multiple segments of different axonal segments[16]. It is perhaps with regard not simply to actual loss of myelin but also to an active oligodendrocyte loss that there would develop remissions and relapses evolving as multiple sclerosis. Multiple axonal segments as separate myelin sheaths account for programmed cell loss that bypasses an apoptotic cell death event. Such cell loss might involve lysis rather than a programmed cell apoptotic pathway. However, oligodendrocyte cell loss might result specifically from a disease process culminating as a demyelinated MS plaque. Multiplicity of lesion infliction would characterize an oligodendrocyte cell loss inducing apoptotic cell death or lysis. On the other hand, the proremyelinating effects of systemically administered Insulin Growth Factor-1 are unlikely to result from direct effects on the oligodendrocyte lineage[17].

Oligodendrocyte lysis and oligodendryocyte dysfunction may involve depletion of the cell population in terms of nonreactivity of subcellular organelles or membranes. Progressive depletion of viable cells involved in myelination would implicate lesions beyond simple progression of a specific cell injury. A one-hit biochemical model has however been proposed for many neurodegenerative states whereby a mutant steady state involves a single event in randomly initiating cell death[18].

A threshold event that induces loss of viability of oligodendrocytes might entail dedifferentiation to an astrocytic phenotype. Neuronal cell loss would evolve not simply as cell death but especially as dedifferentiation events affecting viability of cell subsets. Neuronal cell death as a program of predetermined availability and functionality would involve more than just apoptoses of cells. Differentiation of cells such as neurons or oligodendrocytes might induce potentially increased cell susceptibility to injury. While mRNAs for all three cyclin dependent kinase 5 activators are expressed in substantia nigra during development, only p35 protein is expressed in apoptotic profiles. Cdk5/p35 expression is possibly commonly implicated in apoptotic neuronal cell death[19].

Neuronal cell loss would apply as a process that involves more than just dynamics of cell lysis. Cycles of demyelination and remyelination might constitute effective resolution of a cell injury in multiple sclerosis that permits further oligodendrocyte injury. Indeed, redefining loss of differentiation of oligodendrocytes as loss of oligodendrocytes and of myelin would lead to a multiple sclerosis process that promotes complete loss of the myelin sheaths in a plaque. Actual plaque evolution as structured progression may transform the differentiated oligodendrocytes to a poorly differentiated astrocytic cell with little or no myelinating potential.

Cycles of disease activity would implicate oligodendrocyte cell loss that result in lost differentiating potential of the oligodendrocytes. Oligodendrocytic survival is closely tied up with myelin production around axonal segments. Myelination may evolve enwrapped axonal as transformed myelinated axons that integrally affect nerve impulse conduction. Lymphocytic targeting of myelin sheaths would implicate demyelination resulting also from dedifferentiation of the parent oligodendrocyte. Transformation differentially affecting oligodendrocytes can result in loss of myelin sheaths as MS plaques enlarge, remit and relapse with disease progression.

Age-related patterned cell loss in Alzheimer's disease: Alzheimer's disease as a hippocampus-based disease process would progress largely as a cell loss that is selectively patterned and as an age-related brain atrophy. Lipid proteolysis, neurofilament dystrophy and synaptic loss may promote cell loss primarily generated as an atrophy that is age-related. A continuum of the longest adult tau isoform plus the domain of exon 6 significantly inhibits neurite elongation during cellular differentiation and formation of neurofibrillary tangles and neurodegeneration[20].

Increasing age results in a type of brain atrophy of Alzheimer type that might allow the drawing up of criteria that contrast with those of simple senile brain atrophy. The hippocampus is a site for evolving histopathologic changes affecting, in predilected fashion, the senile atrophic brain, and also potentially destroying large populations of selectively vulnerable neurons. Synaptic loss is the best neurobiologic correlate of cognitive deficits in Alzheimer's disease. There is also evidence of decreased transcripts related to synaptic vesicle trafficking in this disorder[21]. The selectively dementing nature of Alzheimer's disease is related to an involvement of hippocampi that subsequently progresses as atrophy of age-related type. In this context, Alzheimer-type dementia is a process of senile atrophy that selectively wipes out whole neuronal regions in cerebral cortex and leads to hippocampal involution.

Alzheimer's disease as a spreading tissue involution might account for interaction between cells that are eventually lost or else develop dystrophic neurites or neurofibrillary tangles. A developmental shift in tau isoform expression may lead to loss of function due to abnormal tau inducing abnormal microtubule dynamics, neuronal cell death and dementia[22]. This effective interaction between differentially affected neuronal subpopulations would evolve as involuting brain atrophy. Interactivity might account for a selectivity of cell loss affecting a cerebral cortex that atrophies to the point of tissue involution.

Systemic embryonic pathogenesis in neuronal cell loss and myofiber atrophy in ALS: Motor neuron disease as a progressive atrophy of skeletal myofibers would incorporate not only neurofilament degeneration but also trans-synaptic transfer of injurious agents.

Axotomised neuromuscular junctions in Wld(S) mutant mice offer an opportunity for experimental elucidation of developmental mechanisms of synaptic regression involving asynchronous synapse withdrawal[23].

The full-blown disease process is one that primarily targets the motor-neuronal pathways as systems of atrophy both of the neuronal cell body and the denervation of multiple skeletal muscle groups. These may pathologically affect much of the motor neuronal projection system. Extension to the motor cerebral cortex follows ascending spinal cord involvement. Such a phenomenon of extension may result from toxicity to neural cells that progress as transfer phenomena. Initiation of an atrophic process that develops subsequent to myofiber denervation might help account for a pathway degeneration whereby both neuron and myofiber share features of a cell atrophy phenomenon. A skeletal myofiber may share with neuronal degeneration a common endpathway progressing as variable involvement of the motor system. Degenerative atrophy might contribute to formulated patterns of primary neuronal cell death implicating oxidative stress. Trans-synaptic transmission of a disease process at neuromuscular junctions would participate with a concurrent skeletal myofiber atrophy that extends to involve other groups of myofibers further afield.

Involvement of distal muscles of the lower limb resulting within a few years in respiratory muscle paralysis might show constant patterns involvement linked directly to a neuromuscular pathology as a lesion of progression. It is the delineation of an essential neuronal cell loss affecting the anterior horns of gray matter of the spinal cord that would account for a concurrent skeletal myofiber atrophy.

Primary motor neuronal cell loss might account for extension to the primary motor cortex as progressive lesions in at least some patients. Pathologic cell death arising from oxidative stress would lead to the development of neurofilament skeins or inclusions within anterior horn neurons and also neurofilament degeneration of axons. Motor neuron disease as a failure of maintained axonal viability would incorporate also progressive skeletal myofiber loss of whole muscle groups. A neuropathy and a primary neuronopathy of the anterior gray horns of the spinal cord would implicate progressive denervation atrophy of myofibers concurrent with loss of neuromuscular synaptic junctions.

A whole series of concurrent processes that differentially affect the neurons in primary motor cortex and anterior spinal gray horn and also skeletal myofibers may progress as cascade-type events[24]. An initial stage in development of the disease process would primarily affect muscle in terms mainly of the neuromuscular junction and also of skeletal myofibers as initial pathologic events.

Loss of viability of anterior horn neurons as a group concurrent with a primary myopathic process of initiation would necessarily include denervation atrophy that evolves. A distinctive stage of the disease develops as established progressive loss of whole groups of anterior horn neurons.

Essential loss of neurons might implicate pathologic transfer resulting in skeletal myofiber atrophy. Vulnerability of neurons as myofiber atrophy might arise not simply on the basis of exposure of the cells to a toxic agent but especially as progressive atrophy beyond directly induced effect. Motor system atrophy as a cellular series of primary insults would progress as transforming attributes of such injury. Nerve Growth Factor triggers the formation of neurites during differentiation of PC12 cells as reinforced propensity for apoptosis, with increased risk for neuronal cell death that is linked to potential regeneration[25].

Integral loss of motor and voluntary control of skeletal muscle contractility may influence relentless progression of the disease process. An analogy to Parkinson's disease appears not applicable to the progression of adult motor neuron disease even though motor pyramidal and extrapyramidal pathways appear to be both purely integral pathways of progression. In this manner, intermediate products of alpha-synuclein aggregation cause death of susceptible dopaminergic neurons as a critical event in development of Parkinson's disease and other synucleinopathies[26].

Transforming applicability in terms of the action of toxic or infectious agents does not appear implicated as two disease processes progressing as a primarily oxidative stress pathogenesis.

Although Parkinson's disease may implicate a significant dementia in terms not usually applicable to adult neuron disease, it is instructive perhaps to recognize the combined Amyotrophic Lateral Sclerosis/Dementia Complex of Guam that traditionally has been interpreted as a composite of two primary disorders. It might be significant to consider motor neuron disease as purely a system pathway at times inherently implicating neuronal cell loss of other system pathways. Such a paradoxical situation might directly progress as a simple neuronal cell loss reflecting the true nature of disease pathogenesis.

Alzheimer's disease, on the other hand, appears associated with reactivated developmental programs that do not correlate with a differentiated neuronal background, thus potentially resulting in cell death[27]. Neuronal cell loss in ALS has traditionally been interpreted as implicating various cell injuries incorporating also denervation atrophy of skeletal myofibers. Neuronal cell loss and myofiber atrophy are primary expressions of an embryologically related series of early events in development of the fetus.

Embryonic pathogenesis in neuronal cell death: Embryonic pathogenesis in neuronal cell death might bridge developmental process dynamics implicating cell fate determination beyond just agenesis or hypoplasia. Dynamic changes in gene expression profiles follow axotomy of projection CNS fibers incorporating a postaxotomy transcriptional program[28].

The adult onset of motor neuron disease parallels in some essential ways an analogous motor system disease of myofiber denervation of infantile Werdnig Hoffman type. Recurrence of infantile and juvenile cases of motor neuron disease would contrast with a much later onset for progressive cell loss in Parkinson's disease[29]. In Parkinson's disease, synaptic dysfunction may possibly result from axonal pathology as also noted in the hippocampus and amygdala of these patients[30].

Essential neuronal cell loss arising as an embryonic pathogenesis would initiate pathways of progression independent of actual age of the individual. In this sense, perhaps, loss of anterior spinal gray horn neurons would evolve as a primary lesion in a manner that sharply contrasts actual disease dynamics with clinical presentation and even progression. Motor neuron disease might bridge disease categorization that is age-related origin with a clinical evolution in its own right. Perhaps motor neuronal cell loss in ALS is inherently embryonically predetermined and arising as a partly independent variable of the clinical progression.

A defect in the retinoid signaling pathway may be partly responsible for some types of motoneuron disease, as through loss of expression of the retinaldehyde dehydrogenase enzyme II in motoneurons[31].

Indeed, neurodegenerative disorders that span a spectrum of clinical presentations as progression of multiple sclerosis type, of organic dementia of Alzheimer type, of Parkinson's disease and of motor neuron type would all imply systems of involvement of specific neuronal subtype of embryonic determination. It is in terms of such embyronic predestined programming of neuronal cell viability and susceptibility or of oligodendrocyte loss that one might account for neurodegeneration and demyelination beyond simple cause-effect pathogenesis in cellular organelle or system pathology.

REFERENCES

1. Ladefoged, O., K.S. Hougaard, U. Hass and I.K. Sorensen *et al.,* 2004. Effects of combined prenatal stress and toluene exposure on apoptotic neurodegeneration in cerebellum and hippocampus of rats. Basic Clinical Pharmacology Toxicology, 94: 169-76.
2. Greenfield, S. and D.J. Vaux, 2002. Parkinsons disease, Alzheimers disease and motor neuron disease: Identifying a common mechanism. Neuroscience, 113: 485-92.
3. Bredesen, D.E., P. Mehlen and S. Rabizaldeh, 2004. Apoptosis and dependence receptors: A molecular basis for cellular addiction. Physiol. Rev., 84: 411-30.
4. Sendtner, M., G. Pei, M. Beck, U. Schweizer and S. Wiese, 2000. Developmental motoneuron cell death and neurotrophic factors. Cell Tissue Research. 301: 71-84.
5. Cowen, T., 2002. Selective vulnerability in adult and ageing mammalian neurons. Auton. Neurosciences, 28: 20-4.
6. Watts, R.J., O. Schuldiner, J. Perrino, C. Larsen and L. Luo, 2004. Glia engulf degenerating axons during developmental axon pruning. Curr. Biology, 20: 678-84.
7. Geloso, M.C., V. Corvino, V. Cavallo and A. Toesca *et al.*, 2004. Expression of astrocytic nestin in the rat hippocampus during trimethyltin-induced neurodegeneration. Neuroscience Letters, 4: 103-6.
8. Kinugasa, T., S. Ozaki, S. Hamanaka and N. Kudo, 2002. The effects of sciatic nerve axotomy on spinal motoneurons in neonatal Bax-deficient mice. Neuroscience Research, 44: 439-46.
9. Young, C., T. Tenkova, K. Dikranian and J.W. Olney, 2004. Excitotoxic versus apoptotic mechanisms of neuronal cell death in perinatal hypoxia/ischemia. Curr. Mol. Med., 4: 77-85.
10. Carloni, S., E. Mazzoni and W. Baldunini, 2004. Caspase-3 and calpain activities during the rat brain growth spurt. J. Neurochem., 89: 197-203.
11. Hamet, P. and J. Tremblay, 2003. Genes in aging. Metabolism, 52: 5-9.
12. Kretzschmar, D. and G.O. Pflugfelder, 2002. Glia in development, function and neurodegeneration of the adult insect brain. Brain Research Bulleton, 57: 121-31.

13. Zhang, S., L. Xu, J. Lee and T. Xu, 2002. Drosophila atrophin homolog functions as a transcriptional corepressor in multiple developmental processes. Cell, 108: 45-56.
14. Ulbrich, M., V.C. Schmidt, M. Ronsiek and A. Mussmann *et al.,* 2002. Genetic modifiers that aggravate the neurologic phenotype of the wobbler mouse. Neuroreport, 25: 535-9.
15. Engidawork, E., N. Balic, J.F. Juranville, M. Fountoulakis, M. Dierssen and G. Lubec, 2001. Unaltered expression of Fas (CD95/APO-1), caspase-3, Bcl-2 and annexins in brains of fetal Down syndrome: Evidence against increased apoptosis. J. Neural. Transm. 61: 149-62.
16. Sporkel, O., T. Uschkureit, A. Bussow and W. Stoffel, 2002. Oligodendrocytes expressing exclusively the DM20 isoform of the proteolipid protein gene: Myelination and development. Glia, 37: 19-30.
17. OLeary, M.T., G.L. Hinks, H.M. Charlton and R.J. Franklin, 2002. Increasing local levels of IGF-1 mRNA expression using adenoviral vectors does not alter oligodendrocyte remyelination in the CNS of aged rats. Mol. Cell Neuroscience, 19: 32-42.
18. Clarke, G., R.A. Collins, B.R. Leavitt and D.F. Andrews *et al.*, 2000. A one-hit model of cell death in inherited neuronal degenerations. Nature, 13: 195-199.
19. Neystat, M., M. Rzhetskaya and N. Kholodilov *et al.*, 2001. Expression of cyclin-dependent kinase 5 and its activator p35 in models of induced apoptotic death in neurons of the substantia nigra *in vivo.* J. Neurochem., 77: 1611-25.
20. Luo, M.H., M.L. Leski, A. Andreadis, 2004. Tau isoforms which contain the domain encoded by exon 6 and their role in neurite elongation. J. Cell Biochem., 91: 880-95.
21. Coleman, P.D. and P.J. Yeo, 2003. Synaptic slaughter in Alzheimers disease. Neurobiology Aging, 24: 1023-7.
22. Bunker, J.M., L. Wilson, M.A. Jordeu and S.C. Feinstein, 2004. Modulation of microtubule dynamics by tau in living cells: Implications for development and neurodegeneration. Mol. Biol. Cell, 15: 2720-8.
23. Gillingwater, T.H. and R.R. Ribchester, 2003. The relationship of neuromuscular synapse elimination to synaptic degeneration and pathology: Insights from WldS and other mutant mice. J. Neurocytol., 32: 863-81.
24. Froestl. W., 2000. Receptors in neurodegenerative diseases. Pharm Acta Helv., 74: 247-51.
25. Mielke, K. and T. Herdegen, 2002. Fatal shift of signal transduction is an integral part of neuronal differentiation: JNKs realize TNFalpha-mediated apoptosis in neuronlike, but not naïve, PC12 cells. Mol. Cell Neuroscience, 20: 211-24.
26. Robertson, D.C., O. Schmidt, N. Ninkina, P.A. Jones, J. Sharkey, V.L. Buchman, 2004. Developmental loss and resistance of MPTP toxicity of deopaminergic neurons in substantia nigra pars compacta of gamma-synuclein, alpha-synuclein and double alpha/gamma-synuclein null mutant mice. J. Neurochem., 89: 1126-36.
27. Arendt, T., 2001. Alzheimers disease as a disorder of mechanisms underlying structural brain self-organization. Neuroscience, 102: 723-765.
28. Abankwa, D., P. Kury and H.W. Muller, 2002. Dynamic changes in gene expression profiles following axotomy of projection fibers in the mammalian CNS Mol. Cell Neurosci, 21: 421-35.
29. Jackson-Lewis, V., M. Vila, R. Djaldetti and C. Guegan, *et al.*, 2000. Developmental cell death in dopaminergic neurons of the substantia nigra of mice. J. Comp. Neurol. 28: 476-88.
30. Bertrand, E., W. Lechowicz, E. Lewandowskaand G.M. Szpak *et al.*, 2003. Degenerative axonal changes in the hippocampus and amygdala. In: Parkinsons Disease Folia Neuropathol., 41: 197-207.
31. Corcoran, J., P.L. So and M. Maden, 2002. Absence of retinoids can induce motoneuron disease in the adult rat and a retinoid defect is present in motoneuron disease patients. J. Cell Sci., 15: 4735-41.