Changes of Serum Immune Profile in Hereditary Neuropathies

Magdy Khalaf[1], Faten Farouk[2]
Departments of Neurology[1], Immunology[2], El-Mataria Teaching Hospital

ABSTRACT

Background: *Hereditary neuropathies were accompanied with several gene mutations, which, also, may lead to affect their immune serum profile.* ***Purpose:*** *Assessment of serum immunoglobulin and complement changes in children with hereditary neuropathy aged 6-12 years.* ***Patients and Methods:*** *30 children aged 6-12y, suffering from hereditary neuropathy and 10 normal control matched children. Quantitative determination of human serum proteins IgM, IgG, IgA, C3c and C4 using turbidimetric peak-rate method assessment, were done in the 40 subjects.* ***Results:*** *IgM, IgG, C3c and C4 were significantly affected in neuropathic children compared to normal control group.* ***Conclusion:*** *In conclusion serum immune profile abnormalities were identified in different types of hereditary neuropathic children.* **(Int. J. Ch. Neuropsychiatry, 2004, 1(1): 75-82)**

INTRODUCTION

Cells of the immune system possess elaborate systems of proteins that unable them to respond to signals that are: self generated, derived from other immunocytes, conveyed by the neuroendocrine and autonomic nervous systems. Most of these signals are generated and interact with specific receptors in the plasma membrane or inside the target cells, this activates a cascade of protein systems e.g.: protein kinases, protein phosphatase, binding proteins and intracellular proteins. So either cell biochemistry or gene expression were affected to bring about a change in immune cell function[1]. The pathologic findings of most of hereditary neuropathy are those of an axonal type with fiber loss and multiple onion bulb more prominent in distal rather than in proximal nerves[2], this leads to uniform slowing in nerve conduction. Impairment of the regulators of neurotrophins or their receptors has been postulated to be relevant in neuropathies, so high titer of immunoglobulins and complement C3c and C4 lead to prevent neurotrophic activity that up regulate nerve varicosities and disturb its functions[3]. PMP22 on chromosome 17p.11.2, MPZ(PO) on chomosome1q22-23, NDRG2 on 8q24.3, Cx32 on Xq13.4, EGR ch.10q21.1-22.1, 5q23-33, 1p35-36, 3q13-22, 7p14, and NF-L8p21 were examples of genetic affection in cases of hereditary neuropathy[4]. Serum auto antibodies are the markers for immune-mediated suggested adequacy of treatment when titer was reduced more than 60%, also

increase IgM auto antibodies –associated neuropathies are difficult to treat using immune suppressive drugs[5], immune system participates in modulating nervous system connections and its functions, so our study is to evaluate the relationship of serum immune profile and different types of hereditary neuropathies[5].

PATIENTS AND METHODS

The study was carried in Department of Neurology in El-Mataria Teaching Hospital, 30 children patients aged 6-12 years old 15 males and 15 females presented by progressive motor and sensory dysfunction of peripheral nerves in more than one limb, 4 patients of them had mixed sensory and autonomic dysfunction,10 control normal matching group 5 males and 5 females.

Our inclusion criteria:

1. Normal prenatal and postnatal history
2. Normal mental development
3. Motor, sensory or autonomic dysfunction.

Exclusion criteria:

1. Abnormal and difficulties in pregnancy and labor.
2. Intellectual affection.
3. History of metabolic, infections and head trauma underlying the disease process.

All 40 children were subjected to:

1. Thorough neurological and medical examination.
2. Total neuropathy score[6].
3. *Neurophisiological examination:* electromyography and nerve conduction velocity in at least two nerves.
4. *Immunological laboratory examination:* Reagents containing antiserum for the quantitative determination of human serum proteins were used in this study. In this immunochemical reaction the proteins contained in the human serum samples form immune complexes with the specific antibodies of the reagent. The turbidity generated in the reaction is measured photo metrically. The concentrations present are determined quantitatively by turbidimetric measurement of the maximum reaction velocity (peak-rate method), the maximum reaction velocity of precipitate formation and the time taken to be reached are measured simultaneously.

Statistical analysis

Data entry was done using Epi-Info 6.04 computer software package, while statistical analysis was done using SPSS 11.0 statistical software package. Data were presented using descriptive statistics in the form of frequencies and percentages, and mean and standard deviation. Quantitative continuous data were compared using Student t-test. Qualitative variables were compared using chi-square test. Whenever the expected values in one or more of the cells in a 2x2 tables was less than 5, Fisher exact test was used instead. Statistical significance was considered at P-value <0.05.

RESULTS

Table 1. Age and diagnosis of patients in the study sample (n=30).

	Frequency	Percent
Age (years):		
Range	6.0-12.0	
Mean±SD	8.8±2.0	
Diagnosis:		
Sensory motor	26	86.7
HSAN	4	13.3

Table 2. Comparison of Ig and complement abnormalities in patients and control.

	Group				Chi-Square Test	p-value
	Case (n=30)		Control (n=10)			
	No.	%	No.	%		
IgM:						
Normal	9	30.0	10	100.0		
High (>370)	21	70.0	0	0.0	Fisher	<0.001*
IgG:						
Normal	8	26.7	10	100.0		
High (>450)	22	73.3	0	0.0	Fisher	<0.001*
IgA:						
Normal	22	73.3	10	100.0		
High (>1700)	8	26.7	0	0.0	Fisher	0.17
C_3c						
Normal	9	30.0	10	100.0		
High (>90)	21	70.0	0	0.0	Fisher	<0.001*
C_4						
Normal	6	20.0	10	100.0		
High (>40)	24	80.0	0	0.0	Fisher	<0.001*

* Statistically significant

Table 3. Comparison of Ig and complement abnormalities in patients according to age.

	Age (years)				Chi-Square Test	p-value
	<10		10+			
	No.	%	No.	%		
IgM:						
Normal	3	15.0	6	60.0		
High (>370)	17	85.0	4	40.0	Fisher	0.03*
IgG:						
Normal	2	10.0	6	60.0		
High (>450)	18	90.0	4	40.0	Fisher	0.007*
IgA:						
Normal	14	70.0	8	80.0		
High (>1700)	6	30.0	2	20.0	Fisher	0.68
C_3c						
Normal	2	10.0	7	70.0		
High (>90)	18	90.0	3	30.0	Fisher	<0.001*
C_4						
Normal	1	50.0	5	5.0		
High (>40)	19	95.0	5	50.0	Fisher	0.009*

* Statistically significant

Table 4. Comparison of Ig and complement abnormalities in patients according to gender.

	Gender				Chi-Square Test	p-value
	Male		Female			
	No.	%	No.	%		
IgM:						
Normal	5	33.3	4	26.7		
High (>370)	10	66.7	11	73.3	Fisher	1.00
IgG:						
Normal	6	40.0	2	13.3		
High (>450)	9	60.0	13	86.7	Fisher	0.21
IgA:						
Normal	10	66.7	12	80.0		
High (>1700)	5	33.3	3	20.0	Fisher	0.68
C_3c						
Normal	4	26.7	5	33.3		
High (>90)	11	73.3	10	66.7	Fisher	1.00
C_4						
Normal	3	20.0	3	20.0		
High (>40)	12	80.0	12	80.0	Fisher	1.00

Table 5. Comparison of Ig and complement abnormalities in patients according to diagnosis.

	Diagnosis				Chi-Square Test	p-value
	Sensory-motor		HSAN			
	No.	%	No.	%		
IgM:						
Normal	6	23.1	3	75.0		
High (>370)	20	76.9	1	25.0	Fisher	0.07
IgG:						
Normal	5	19.2	3	75.0		
High (>450)	21	80.8	1	25.0	Fisher	0.049*
IgA:						
Normal	20	76.9	2	50.0		
High (>1700)	6	23.1	2	50.0	Fisher	0.28
C_3c						
Normal	6	23.1	3	75.0		
High (>90)	20	76.9	1	25.0	Fisher	0.07
C_4						
Normal	3	11.5	3	75.0		
High (>40)	23	88.5	1	25.0	Fisher	0.02*

* Statistically significant

Table 6. Quantitative comparison of Ig and complement abnormalities in patients according to diagnosis.

Mean±SD	Diagnosis		t-test	p-value
	Sensory-motor (n=26)	HSAN (n=4)		
IgM	476.7±147.3	287.5±131.5	2.42	0.02*
IgG	580.0±143.5	437.5±149.3	1.84	0.08
IgA	1229.2±402.5	1600.0±294.4	1.76	0.09
C_{3C}	127.8±34.5	90.0±21.6	2.11	0.04*
C_4	64.0±16.2	45.0±17.3	2.17	0.04*

* Statistically significant

DISCUSSION

Lymphoid organs and tissues comprise heterogeneous mix of lymphoid and myeloid cells residing in a reticular storm that provides a supporting framework. Norepinephrine, cholinergic, and peptidergic nerve fibers distribute to both primary and secondary lymphoid organs among cells of the immune system. Cells of the immune

system communicate by means of hundreds of kinds of signaling molecules that are secreted by exocytosis, diffuse through the plasma membrane to be released into the extra cellular fluids and remain tightly bound to the cell surface and influence only cells that contact the signaling cell[7]. The nervous system communicates with cells of the immune system through the evoked release of neurotransmitters, neuromodulators, and hormones. Secreted signaling molecules from these two interactive systems include a variety of structurally different substances, including proteins, small peptides, amino acids, nucleotides, trophic factors and dissolved gases. Complement, the complex series of proteins and glycoproteins are capable of generating a broad series of inflammatory actions including cell lysis, chemo taxis, opsoniztion and certain anti-inflammatory effects, complement is present in all body fluids except cerebrospinal fluids and urine, antibodies binds target antigen through Fab position and the exposed Fc part fixes the complement, a cascade of complement interaction followed by C3 cleavage and sequential addition of other complement C4, this lead to formation of membrane attach complexes which form pores in target cells[8]. The main relevance of complement activation in the context of inflammatory brain disease may therefore be the breakdown of C3, releasing membrane bound and fluid phase products which determine interactions between oligodendrocytes, Shawnn cell and macrophages or microglia[9]. Vander Laan et al, confirm that uptake of myelin by macrophages enhanced on opsonization with complement, involve the CR3 receptor, induce a rise in intracellular calcium, and are associated with the production of TNFα and nitric oxide by these activated macrophages[10]. The general principle that the signals transuded by cells during growth and physiological activity are the same as those which become overloaded during pathological events leading to cell injury and death, the extent to which a cell can survive injury is modulated by its growth-factor-dependent state of health[11]. It follows that cell death may occur in response to a state of injury from which protection would be anticipated under more favorable growth factor conditions and conversely optimal growth factor conditions may save cells from otherwise lethal events occurring at the cells membrane[11], this explained the significant statistically positive correlation ($p<0.05$) between the early age of both sexes and immunoglobulins and complement abnormalities (table 3) with no statistically difference regarding patient gender ($p=0.5-1$), (table 4). Non-compact myelin is found in paranodes (the lateral borders of the myelin sheath) and in Schmidt-Lanterman incisures. It contains junctional specializations between the layers of the myelin sheath, so-called "reflexive" or "autotypic" junctions[12]. Some of these reflexive junctions are also found in inner and outer mesaxons. Adherens junctions are most numerous in the outer mesaxon as well as in outermost layers of the paranodes and incisures; these contain E-cadherin, α-catenin, and β-catenin, and are likely linked to the actin cytoskeleton). Tight junction strands enclosing gap junction-like plaques have been found by freeze fracture electron microscopy. The claudin(s) forming these tight junctions remains to be determined[11]. IgM are the first immunoglobulins appear in immune system and it is associated with chronic motor neuropathy which has binding specificity for

motor neuropathy syndrome in 97% of cases and IgM deposits impregnated in the inner layer of the perinerium so affect paranodes and non compact myelin, IgG and IgM increase in wide spread distal axonal degeneration, IgA increase in acquired type explained on basis of persist antigenic stimuli as viruses or bacteria secondary to phagocytic dysfunction resulting in antigen driving polyclonal B-cells activation, also presence of micro or macro angiopathy are associated with a significant increase in serum IgA concentration[13] and IgG are frequently antibodies made after rechallenge of the host with antigen, also deposition of complement occurred on the axonal surface of schwann cell[14] (tables 5, 6), C4 increase in neuropathy accompanied with other deficits (table 6), this affect the paranodal glial loops contain neurofascin 155, which likely interacts with heterodimers composed of contactin and Caspr/paranodin to form septate-like junctions[15]. The juxtaparanodal axonal membrane contains the potassium channels Kv1.1 and Kv1.2, their associated β 2 subunit, as well as Caspr2. Kv1.1, Kv1.2, and Caspr2 all have PDZ binding sites and likely interact with the same PDZ binding protein. Like Caspr, Caspr2 has a band 4.1 binding domain, and both Caspr and Caspr2 probably bind to the band 4.1B isoform that is specifically found associated with the paranodal and juxtaparanodal axolemma. When the paranode is disrupted by mutations (in cgt-, contactin-, and Caspr-null mice), the immune interaction, the localization of these paranodal and juxtaparanodal proteins is altered: Kv1.1, Kv1.2, and Caspr2 are juxtaposed to the nodal axolemma, and this reorganization is associated with altered conduction of myelinated fibers[16]. So understanding how axon-Schwann interactions create the molecular architecture of myelinated axons is fundamental and almost certainly involved in the pathogenesis of peripheral neuropathies.

Conclusion

In summary, the intricate localization of numerous axonal proteins is highly related to the structure of the overlying myelin sheath. This organization is disrupted by a number of mutations that affect various components of the myelinated axons, and its functional consequences, axon-Schwann interactions create the molecular architecture of myelinated axons which is fundamental and almost certainly involved in the pathogenesis of peripheral neuropathies. So, serum immune profile abnormalities which were identified in different types of hereditary neuropathies appeared to be primary affection of this myelinated axons and membrane hyperpolarization which occurred secondary to deficiency of inward rectification that pass cation into the axon on hyperpolarization.

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