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A CASE REPORT WITH 18 EPISODES OF BACTERIAL MENINGITIS DUE TO C3 DEFICIENCY.

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In previous studies some investigators have indicated a rare but informative deficiency of C3, which is associated with increased susceptibility to severe life threatening infections by pyogenic micro-organisms(1,2,3) in particular pneumococcal infections.

Deficiency of C3 component which is the most important of these proteins, due to its central role in both classical and alternative pathways, and biological effects of its fragments, lead to severe and life threatening recurrent infections.

The first case report of C3 deficiency associated with recurrent infection by pneumococcal and klebsiella agents are described by Alper and his coworkers in 1972 (4).

The cases of congenital C3 deficiency reported by Ross and Densen(5) were either secondary to collagen vascular disease, such as SLE, or Primary C3 deficiency which developed into recurrent infections, such as bacterial meningitis. In this report we are presenting a 20 year old male patient who had 18 episodes of meningitis due to congenital deficiency of C3 during 1961 to 1982, mostly pneumococcal meningitis.

Material and Methods:

Our patient with C3 deficiency, who has been followed up in department of immunology and allergy of Tehran University since 1961 was referred to our department, because he had recurrent bacterial meningitis.
He is the 5th child of a closly related parents of whom three, one girl and two boys have died due to meningitis.

According to his medical records, he had 18 attaeks of pneumococal meningitis several episodes of pneumonia, and otitis media.

Humoral and cell-mediated investigations were performed on him and his family. Immunoglobulins and complement were measured, using the single radial immunodiffusion technique(5). B-cells were counted using immunoflurescence method(6) T-cells were counted by SRBC-Rosett technique(7).

Polymorphonuclear phagocytic activity test(bacterial kling) by NBT(8), Chemotaxis by Boyden modified procedure (9), and opsonization test by the method of Levinsky,and Harvey (10).

Case report:

A Case Report With 18 Episodes OF

SH.KH. a 20 year old male was admitted to hospital during the 18th episodes of meningitis, in May 1982,with fever, vomiting and headache. According to his medical records he had since 1961, when he was 10 months) till 1982 (the last admission), 18 episodes of bacterial meningitis, pneumonia, and purulant otitis media. As shown in table 1:

Date	Age	Episodes	Clinical findings	Laboratory findings
1961	10m.	first	bacterial meningitis	Dipl.Pneum.in CSF
1963	2y.	second	Pneumonia+meningitis	" " "
1966	4y.	3rd.	Pneum.meningitis	" " "
1967	5y.	4th	Bacterial meningitis+otit	" " "
1967	5y.	5th	second episode meningitis	" " "
1968	6y.	6th	meningitis+mastoiditis	" " "
1969	8y.	7th	Bacterial meningitis	" " "
1970	9y.	8th	" "	" " "
1972	11y.	9th	Pneumonia+meningitis	" " "
1972	11y.	10th	" "	" " "
1973	12y.	11th	" "	" " "
1973	12y	12th	" "	" " "
1975	14y.	13th	Bacterial meningitis	" " "
1975	14y.	14th	" "	" " "
1975	14y.	15th	" "	" " "
1978	17y.	16th	" "	" " "
1980	19y.	17th	" "	" " "
1982	20y.	18th	Bactrial meningitis	Pneumococcus.

During the last hospitalization, we investigated more to find out the actual cause of the recurrent meningitis in this patient. We studied not only anatomical defects,such as minor fractures of the skull, dermoid cysts,the cranio-nasal fistula, and absence of spleen(asplenia), which are the commonest causes of the recurrent bacterial meningi-tis, but also we did all immunological tests available to investigate probable immunodeficiency.

Results:

Physical examination: normal appearence, weight 90 kg. Height= +176cm., BP= 120 mmHg,body temperature=39 C. ENT examination showed bilateral perforated otitis media, mastoidectomised scar surgery, left keratitis, and normal fundoscopy of the eyes.

Radiological findings, on several occasions lobar pneumo-nia, once Cardiomegaly were mentioned. Skull Xr perfectly normal, and abdominal C.T.scan ruled out asplenia, which are the common causes of recurrent meningitis.

Laboratory investigations:

C.B.C: WBC=31100, mm3, PMN=77%, L=19%, Band=4%,Hb=13g, Hct=45% CSF examination results: Leukocyte=4500/ml,poly= 80%,lymph=20% Chemistry: protein=300mg/dl, sugar=20mg/dl, smears, and cultures on several times showed diplococcus pneumonia.

Immunological examination: the results of immunological findings which were checked three times are summarized in table 2 and 3.

Tests	First	Second	Third
Immunogl.	IgG 313mg/dl	880mg	547mg/dl.
	IgA 359	290	92
	IgM 144	160	52
Complement			
components:	CH50 20%	Zero	Zero
	Clq	131mg	120mg/dl
	C3 0	0	0
	C4 71		71mg/dl
	C2		94% standard
	C5		90%
	Properdin		72%
	Factor I		96%
	Factor H		100%
	Cc Cd		not detectable.

Table 3: Immunological findings:

Test	Patient	Control
T-cell count	71%	70%
B-cell (SmIgs)	22%	38%
Phagocytosis		
NBT	Normal	Normal
Chemotaxis	"	"
Opsonization	Defective	Normal

As shown in table 2and 3, B-cell and T-cell counts were normal in this patient. CH50 activity as tested using Mayers method was zero(defective). The complement components as tested on several occasions showed normal results except for C3 component which was zero(defective), and undetectable by single radial immunodiffusion technique on three occasions.

C1,C4,C2, and C5 were normal.

Properdin, Factor I and Factor H were normal, which means the inhibitor factors are normal.

The phagocytosis activity of PMN,NBT test with stimulated, and unstimulated E-coli Endotoxine (Bacto:LPS-B E-coli 026:B6) and Chemotaxis using Boyden method were normal, but deposition on Zymosan and serum opsonization activity of the patient were absolutly defective.

Looking on the genetic inheritance of C3 deficiency in this patient, studied by family pedigree investigation is shown in the following figure.

The patient's father and mother are cousins and after their close family marriage, they had 6 children, as below:

1) A boy, who died immediatly after birth.

2) A boy, who was the third child of the family and died at five years of age due to meningitis.

3) A girl, who was the fourth child of the family and died at 2 years of age due to meningitis.

4) The first child of the family, a girl who is healthy and 33 years of age, is married to a close family and has a child who has neurofibromatosis.

5) Second child of the family, a male who is healthy and 32 years of age.

6) SH.KH., our case, w ho is the 6th child of the family. Now he is 22 years old and is diagnosed to be C3 deficient.

Patient's father has two brothers and three sisters who are offsprings of unrelated family marriage, he is 55 and healthy. Patients mother is 50, healthy and has 2 brothers and one sister who are offsprings of unrelated family marriage.

Discussion:

Reviewing the literature in the previous decade shows that C3 deficiency and recurrent infections associated with it is relativly rare (Alper & Rosen 1978)(11).

A broad review in this matter is written by Ross & Coworkers (5) who were able to report 14 cases of C3 deficiency, that most of them had recurrent infections due to pneumococcal and Neisseria infections combined with collagen vascular diseases, such as systemic lupus

erythematosis (SLE), vasculitis, and glomerulonephritis. It is not indicated that whether C3 deficiency had primarily caused both recurrent infections and collagen diseases or C3 deficiency is secondry to these disorders, and consequently had led to consumption and catabolism of complement that finaly leads to recurrent infections. However our patient is a very interesting case since firstly recurrent infections mostly were pneumonia and bacterial meningitis,Secondly in all episodes infections were due to Streptococcal Pneumonia, and Thirdly in spite the fact that the patient had 18 episodes of bacterial meningitis he never had the CNS complications or sequellas which are very common in these kind of patients. He is already brillant student, without any disorders in his behaviour.

In addition looking at factors of regulating the complement system either the classical or alternative factors such as I, and H which inhibit the alternative pathway were 96%, and 100% normal. In other words C3 deficiency is a primary cause of the frequent bacterial meningitis, and different to the previous reports(7).

In this patient other factors, which cause recurrent bacterial meningitis such as skull fracture, and presence of fistula in the cranio-nasal septum were studied and ruled out. Congenital absence of the spleen,or splenectomy that can develop to recurrent meningitis was investigated in this case by radiology, and CT. scan, which showed the presence of the spleen, the absence of dermoid cyst on the skull skin was confirmed by neurosurgeon on several occasions.

The opsonisation test in this patient as shown on

Table 3 was defective, which could not be due to the moderately low concentration of IgG (arround 300 mg%), because even 50mg% of this immunoglobulin in serum is sufficient for opsonisation, as mentioned by Soothill (1977). However the only cause for defective opsonization in this case is the absence of C3 component of the complement system.

We should draw the attention to this fact that C3 and its fragments such as C3b, and C3a which are involved in both opsonization activeity, and chemotaxis lead to the pyogenic infections in particular meningitis.

According to the results optained in this patient on Table 2 inhibitor, and activators of the complement system were normal, and undoubtedly C3 deficiency was primary and persistent in this case. The collagen-vascular disorder, and low level of C3 in some cases of glomerulonephritis which cause transient infections were not seen in our patient.

We were not able to test two other children of this family, but most probably they had been C3 deficient that had led to bacterial meningitis, which cause their death during childhood as mentioned above.

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