PERIPHERAL MARKERS OF ALZHEIMER'S DISEASE: SURVEILLANCE OF WHITE BLOOD CELLS

[1]Fatima Shad Kaneez, [2]Yashar Aghazadah, [1]Sagheer Ahmad and [2]Bodo Kress

[1]PAP RSB Institute of Health Sciences, Universiti Brunei Darussalam

Jalan Tungku Link, Gadong BE 1410 Brunei Darussalam

Tel +673 246 3001 ex 2236, mob:6738930806

ftmshad@gmail.com

[2]Chefarzt des Instituts für Neuroradiologie, Krankenhaus Nordwest, Steinbacher Hohl 2-26

60488 Frankfurt

Alzheimer's disease (AD) is a neurodegenerative disorder, which progresses with age and associated with weakening intellectual capacity, spatial disorientation, and memory loss. The observation that the levels of inflammatory markers are increased in AD tissue and are prominently associated with AD lesions (Dickson et al., 1993) has led to the possibility that inflammatory cytokines may play a role in inflammation in the AD brain. Since the resident monocytes in the brain, i.e. microglia produce the inflammatory cytokines, it is possible that elevated levels of activated monocytes precede the development of AD by increasing the permeability of blood brain barrier (BBB) (Strazza et al., 2011). Immunohistochemistry of the AD brain tissue has revealed the co localization of cytokines with activated glial cells (Yamabe et al., 1994).

In order to monitor the disease progression closely and to enhance the accuracy of diagnosis, it is important to identify a highly sensitive and robust inflammatory biomarker of AD. This may also be helpful in early diagnosis of AD when used in combination with other biological markers (Shaw et al., 2007). Literature shows that although the symptoms of AD

appear very late, the process of pathogenesis starts many decades before that (Ray et al., 2007). It is expected that in the coming decades due to increasing life span, the rates of developing AD would be significantly higher (Kinoshita and Clark, 2007).

Therefore, it is necessary to develop highly robust and noninvasive peripheral markers, which possess high sensitivity and specificity, especially for screening those patients who are at risk of developing AD. In this retrospective study, our main objective was to identify peripheral markers in the blood profile of twenty-seven German AD patients diagnosed by MRI. Briefly, all patients included were diagnosed by neuropsychological and CSF tests. MR examinations were done on 1.5T Scanner (Signa, General Electric) performing T2 Fast Spin Echo (FSE), T1 FSE before and after intravenous administration of contrast agent (Magnevist, Schering; Dotarem, Guerbet). Whole blood cell count was done by a whole blood calculator (Advia 120, Bayer). Urine analysis was done by urine analyser (Clinitek Atlas, Bayer diagnostics). Clinical chemistry is done on a Modular analytic EVO analyser (Roche diagnostic).

Following were our main observations after studying the blood reports of these patients:

1. Levels of monocytes in the blood of the diagnosed AD patients were found to be high irrespective of their age and sex (Table 1). For those patients whose monocytes were in normal range their neutrophil levels were considerably high. Whereas blood levels of lymphocytes and basophils were found to be constantly low.
2. Similarly blood glucose and creatinine levels were found to be substantially high, whereas calcium ions were low.

Escalated levels of monocytes and neutrophils are hallmarks of chronic inflammation and may be precursor to AD. A low lymphocyte count specifies that the body's resistance to fight infection is substantially reduced, whereas low basophil levels indicates their over utilization due to chronic allergic inflammatory condition.

Most of the patients in our study were hyperglycaemic and it is known that hyperglycaemia results in increased number of monocytes (Yun et al., 2001). Disturbances in the leukocyte count in these patients suggest chronic inflammation, especially the high monocyte count in most patient means that these monocytes may have detrimental effects on structures such as blood brain barrier (BBB). The disturbances in the calcium profile, which also affects monocytes (Sugimoto et al., 1993), and renal insufficiency. High monocyte levels are also associated in renal disease and this may be the reason for high creatinine level (Wada et al., 1996).

It is likely that activated glial cells which may be subsequent to high monocyte levels, secretes cytokines such as IL-1 and TNFα. These cytokines have been shown to reduce the integrity of BBB by interacting with the brain microvascular endothelial cells (BMEC) as it is the tight packing of these cells which gives characteristic high resistant properties to the BBB. Furthermore, overexpression of these cytokines on the monocyte surface may trigger secretion of cytokines that can do further damage to BBB (Farkas et al., 2006).

Evidence indicating AD as inflammatory disease exhibit that NSAIDs can delay the progression of AD. NSAIDs can also decrease the circulating levels of white blood cells including monocytes and neutrophils. Therefore, it is likely that monocytes and the cytokines

they release are the precursors of the AD pathogenesis. Our study indicates that circulating monocytes and other white blood cells have a relationship with AD. Therefore, WBC count may serve as an early diagnostic marker of AD. This would help, along with other biological markers to detect the patients at risk of AD at an early stage and would give them a better chance for the prevention and delay in the progression of the disease. It should be noted that these are preliminary findings and further detail experiments are needed to confirm the role of white blood cells as peripheral markers of Alzheimer's disease.

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Table 1: Blood profile of twenty-seven diagnosed AD patients

Sex/Age	Monocyte Count /nl	Basophil Count /nl	Neutrophil Count /nl	Eosinophil Count /nl	Lymphocyte Count /nl	Calcium mmol/l	Na mmol/l	Creatinine mg/dl	Glucose mg/dl
M/54	0.62	NA	6.18	0.03	1.23	2.34	143	0.94	121
M/65	0.76	0.04	4.21	0.28	1.89	2.37	144	0.91	114
F/65	0.37	0.02	1.79	0.09	2.12	2.5	142	0.65	92
M/67	0.77	0.01	4.49)	0.13	1.51	2.19	142	1.16	112
F/71	0.74	0.05	4.18	0.07	2.42	2.23	142	0.87	97
M/72	0.37	0.01	8.53	0.07	0.69	2.16	137	0.96	159
F/73	0.58	0.02	4.27	0.15	0.84	NA	142	0.63	81
M/74	1.08	0.03	4.43	0.28	2.13	2.19	139	0.97	128
M/75	1.53	0.01	7.28	0.13	1.08	NA	142	0.94	146
F/75	0.4	0.02	5.02	0.04	1.78	2.3	141	0.84	142
F/76	0.37	0.01	4.17	0.17	1.24	NA	141	0.89	104
M/77	0.46	0.02	3.5	0.11	0.96	2.23	145	1.07	107
F/78	0.39	0.02	4.28	0.06	1.07	2	136	0.74	NA
M/80	1.06	0.03	9.88	0.02	0.68	2.19	145	1.1	175
M/80	0.79	0.03	6.25	0.03	1.22	NA	137	0.63	122
M/81	1	0.02	3.68	0.13	1.73	2.02	142	0.77	121
M/81	0.8	0.03	4.11	0.17	2.07	NA	135	0.71	100
F/82	0.53	0.06	4.19	0.05	1.19	2.31	137	1.21	115
M/84	0.71	0.03	3.83	0.23	1.50	2.17	143	1.18	105
F/85	1.07	0.07	6.56	0.12	0.92	2.32	142	0.8	119
M/86	0.71	0.02	5.66	0.27	1.49	2.1	139	0.6	94
F/87	0.34	0.02	5.2	0.03	0.60	2.24	143	1.24	48
F/88	0.74	0.04	8.37	0.37	2.31	2.27	139	1.3	119
F/89	0.56	0.04	10.05	0.07	1.62	2.16	138	0.68	157
F/89	1.18	0.09	3.43	0.13	0.76	NA	147	0.44	103
F/99	1.1	0.03	5.83	0.07	1.42	NA	134	0.61	97
M/79	0.28	0.03	8.18	0.00	0.55	2.24	143	1.06	112
Normal range	**0.04-0.63**	**0.02-0.10**	**1.92-6.17**	**0-0.38**	**1.32-3.24**	**2.20-2.65**	**135-145**	**0.55-1.10**	**70-110**