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POST-INFLAMMATION VARIANT ALZHEIMER DISEASE (PIvAD): A CLINICAL CASE OF ACUTE ONSET OF DEMENTIA WITH PSYCHOSIS AFTER GENERALIZED SEPSIS AND MAJOR SURGEY

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Abstract

Research suggests that neuroinflammation of the brain has a role in dementia by activating glial cells which then release proinflammatory agents and lipopolysaccharide (LPS) responsible for cognitive deficits. Other authors suggest that there is no clear evidence if neuroinflammation after generalized infection is a cause, agent, or consequence of Alzheimer's Disease (AD) with bacterial endotoxin LPS acting on neurons and microglia. The current case study refers to a 64-year old woman who developed symptoms of dementia and psychosis a month after she was operated for a duodenal perforation resulting in pneumoperitoneum and systemic bacterial sepsis. Neuropsychiatric and clinical assessment gathered the required data. Past psychiatric history was negative for mental health pathologies, and former cognitive deficits were non-existent before the systemic inflammation. Therefore, the authors of the current research speculate that in the case described, systemic inflammation enduringly unlocked dementia, cognitive deficits, and psychosis.

Introduction

There is an increasing proof that inflammation of the brain may be the reason of cognitive deterioration after the activation of microglia and the lysis of Gram-negative bacteria with release of lipopolysaccharide (LPS), probably the major cause for Alzheimer's disease found after generalised infections in animal models [1-3]. It is not clear if the brain neuroinflammation with the release of LPS after systemic sepsis could be a cause or a result of Alzheimer's Disease (AD) with LPS impairing the activity of cerebral neurons and microglia [4,5]. A meta-analysis proposes the influence of neuroinflammation in minor cognitive deteriorations that subsequently might progress to AD [6]. The authors of the current research already reported about the current case of a woman who developed dementia and psychosis after a systemic inflammation and major surgical operation [7]. The authors of the present study speculate the existence of a **Post Inflammation Variant Alzheimer Disease** (PIvAD). Research reports about cases of the impairment of cognitive performances after major surgery with the likelihood of having a short- or long-term progression affecting memory, concentration, verbal fluency, and social skills; the probable cause is neuroinflammation triggered by surgery [8]. Other studies suggest the possibility of neutralizing inflammation of the brain leading to AD in mice with the use of the antibiotic doxycycline proposing its use in humans due to its power to cross the blood-brain barrier [9]. In the PIvADwe speculate that the presentation is irreversible, also after restoring normal health conditions, asepsis, and post-operative homeostasis[7,10].It is likely that a constellation of neuroinflammatory agents identifiable by the Gram-negative bacteria endotoxin LPS and inflammatory cytokines activate macrophages to release lysosomes whch will then alter the blood-brain barrier with activation of local microglia and the beginning of a process of brain neurones apoptosis [11].

Materials and methods

The current case study refers to a 64-year old woman who developed symptoms of dementia and psychosis a month after she was operated for a duodenal perforation resulting in pneumoperitoneum and systemic bacterial sepsis. She was referred to our community psychiatric team by her family doctor. The psychiatric and neuropsychiatric assessment occurred several home visits and utilized unstructured clinical interviews. Our memory clinic also assessed the case index. Several home visits to the patient occurred in the community. During these meetings, the

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leading author (C.L.) conducted the interviews for psychiatric and neuropsychiatric assessment. Each assessment lasted about one hour. Electronic notes obtained clinical records. Collateral information was obtained by the daughter who assisted in providing additional details of the index case. The Magnetic Resonanc images where obtained from the collaborating hospital belonging to the same healthcare trust. The Declaration of Helsinki was used to anonymise all the personal details, to obtain consent, and to reduce possible harm deriving from the assessment.

Results and discussion

Pathological report

The pathological report indicated a perforated duodenal ulcer with the torsion of an ovarian cyst. She had a laparotomy to repair the duodenal ulcer. During intraoperative exploration, surgeons found extensive bilious and purulent contamination with multiple pieces of vegetables. Surgeons also found pus from the wound and intra-abdominal drain. An abdominal CT scan was performed showing marked inflammatory changed around the first and second part of duodenum in keeping with recent perforation.

Neuropsychiatric assessment

1st assessment

During the interview, the patient appeared coherent and appropriate. Her speech was normal in tone, volume and rate. Her daughter reported that mother was misplacing things such as putting sugar into the fridge or struggling to find the real use of familiar objects. Case index also said that when she woke from sleep, she struggled to understand if she was dreaming or not; this occurrence has been described in organic brain disorders and named by one of the authors (CL) 'oneirophrenia.' Authors performed the Addenbrooke's ACE-III test with the following results: Total score 74/100: Attention 18/18, Memory 18/26, Fluency 5/14, Language 20/26 and visuospatial 13/16. Brain MRI showed diffused cortical and subcortical atrophy (**Figure 1**).

2nd assessment

We examined her cranial nerves that were intact, dermographism (recognition of shapes on skin with eye shut) was normal, she maintained right-left orientation, she could name her fingers with eyes closed, she maintained alternate functional movements, she had good fine movement in the finger-nose trial with eyes open and shut, and nose-to-finger trial also intact. Therefore, there seemed to be no cerebellar involvement in her presentation. She was still reporting paraesthesia like 'pins-and-needles' sensation in her lower limbs. The size of her pupils was bilaterally equal and there was no sign of muscular rigidity or unilateral weakness.

3rd assessment

Patient and her daughter reported that word finding was still a problem. Patient was using circumlocutions to specify the meaning of words. The object recognition placed in her hands (coins) with eye shut was intact.

Psychiatric Assessment

Appearance and behaviour

- Good social contact and interaction
- Coherent and appropriate
- No odd actions or agitation
- Fair self-care

Speech

- Normal tone, volume and rate
- No nominal aphasia at the moment of interview
- No pressure or speech or tangential speech

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Thought

- Delusion of reference
- Paranoid delusion about daughter
- Paranoid feelings about food being poisoned
- Paranoid delusions about people
- Recently: though block
- Passivity experiences: people being able to interfere with her mind or command her
- Not reporting thought broadcast or withdrawal

Perceptions

- Second person auditory hallucinations (mostly extra-campine and deriving from people on the road she believed she can hear):
- Voices commenting about her directly with derogatory words as if deriving from people walking out of her house
- Voices commanding her to take her life
- Other auditory hallucinations: hearing people walking on the stair of her house; hearing someone knocking on her door but one was there;
- Tactile hallucinations as if someone was tapping on her shoulders

Insight

- Aware that she was not the same of before
- She felt changed inside
- She would like to improve
- She reported low mood
- She was compliant with medication

Neuropsychological assessment

Memory

Patient said that her memory problem has been there for three-four weeks since her operation. Daughter agreed with this. Patient states she goes into rooms and forgets why she has gone in. She went into fridge to get milk out to find that she had put the milk in the cupboard, and the tea bags put in the refrigerator. Displayed good episodic memory. Could name all the everyday objects in the home.

Attention

Patient stateed that she could only do one thing at a time and the example given was that she would usually eat with her tea on her lap watching television, but that she now could not do this as she would not eat and would only watch the television.

Executive function (Planning and organizing)

She was still doing the housework with some exceptions such as lighting the fire. Generally, she was still able to use household appliances. With an occasional exception such as she tried to make beans on toast, then, she burned the toast and the beans having put their tin in the microwave. She was shopping or taking part in any hobbies because she felt depressed and anxious.

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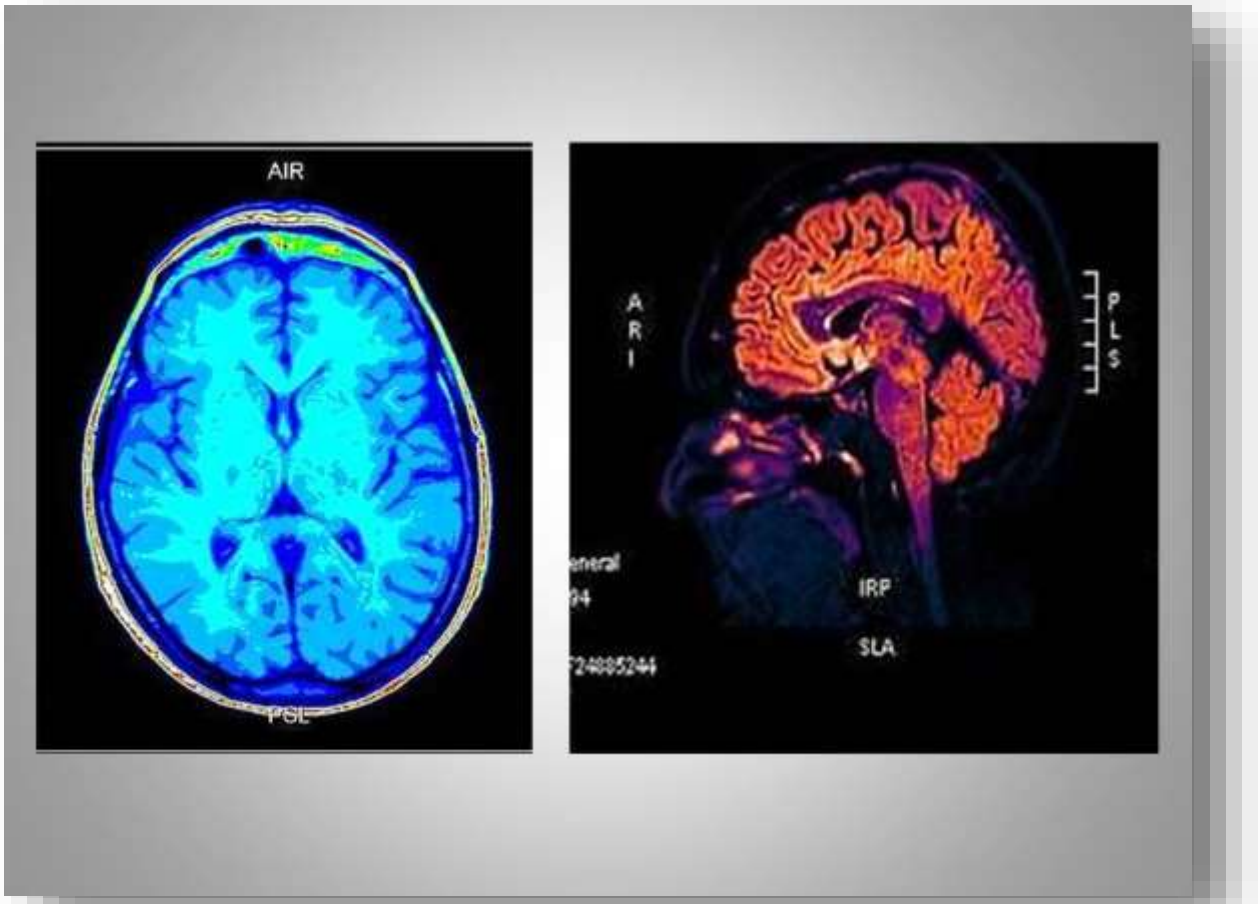

Figure 1: Brain scan of the case index showing some degree of cortical and subcortical atrophy.

Confusion
Patient did not leave the house due to social phobia. She was able to guide assessor around the home from memory and was not confused as to the layout.

Visuo-spatial
Patient stated that she didmisreach for things, but there was no evidence of this while assessor was in the property. She did not misstep or had problems moving from room to room. She had no problems recognizing the faces in photographs.

Language
It was stated that she has never been much of reader but still enjoyed doing crosswords. She showed the assessor a crossword that she was completing. Although the referral identifies word finding difficulties, the day of assessment she was very happy to identify all the common household items present in the room.

Behavioural change
Patient stated that she was stressed out and that she could become a little agitated when she could get her words

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outpatient reported that she was shouting for her daughter when she is on her own, this included waking up daughter when she was on night shift. She admitted this is an unreasonable behaviour. There was some lack of empathy. She withdrew from work events or social engagements.

Discussion

The current case reports highlights that the animal models of brain neuroinflammation and Alzheimer disease has also a correlate in humans as described in the current case. Dementia is known to occur in other human infections inclusive of viruses (e.g., HIV dementia), herpes virus (HSV1), pneumonia (Chlamydophila pneumonia), Spirochete bacteria (Lyme disease)[12]. As reported by Alzheimer's Society if bacteria, viruses or fungi access the brain they can stimulate microglia causing neuroinflammation and with its progression to dementia via death of neurons [12]. In the model reported in the current study and found in animal models, Gram-negative bacterial LPS activates microglia which then progress to cause neuronal loss and dementia (**Figure 2**). More specifically, circulating macrophages activated by generalised sepsis would eventually alter the permeability of the BBB hence allowing neurotoxin LPS and other inflammatory agents to progress to brain tissue hence activating microglia which are responsible for neuronal loss (**Figure 2 and 3**). Surgical stress, and hypothetically any form of severe stress could act similarly by activating an inflammatory response in the body and then triggering a process which mostly resembles that found during bacterial inflammation. It is suggested that chronic emotional stress and Post Traumatic Stress Disorder (PTSD) in veterans also could be linked to cognitive deficits and dementia [13]. The clinical case discussed in the current research and the literature suggests that neuroinflammation conducive to cognitive deficits and Alzheimer's disease are irreversible processes. As also shown in the current case report, an organic psychosis was triggered by the same causes of dementia. Hence, the authors of the current study speculate that the clinical presentation (dementia and psychosis of the case reported) changes according to specific areas of the brain that are targeted by the neuronal loss. Besides, the two conditions, dementia and psychosis, can be comorbid like in the behavioural variant of frontoparietal lobe dementia [14]. The function of microglial cells is multiple while microglial inflammation is considered to be a determinant of brain disease as microglia activated by inflammation determine the destiny of other brain cells [14]. In the current case the major surgery also is hypothesised as a cause of neuroinflammation. It is reported that the production of pro-inflammatory cytokines during major surgery activates dormant microglia into a phagocytic stage with increase of apoptosis of brain cells of Alzheimer disease[15].

Conclusion

The case discussed in the current study suggest the existence of a variant of Alzheimer disease following systematised inflammation which alters blood brain barrier and activates microglia that then start a process of apoptosis of brain neurones. Under the umbrella of neuroinflammation, different causes have been reported in the literature inclusive of bacterial and viral infections, emotional and physical stress, and alteration of gut microbiome. The authors of the current research speculate that the clinical presentation of the human cases following neuroinflammation changes according to the area and extension of the brain which is affected.

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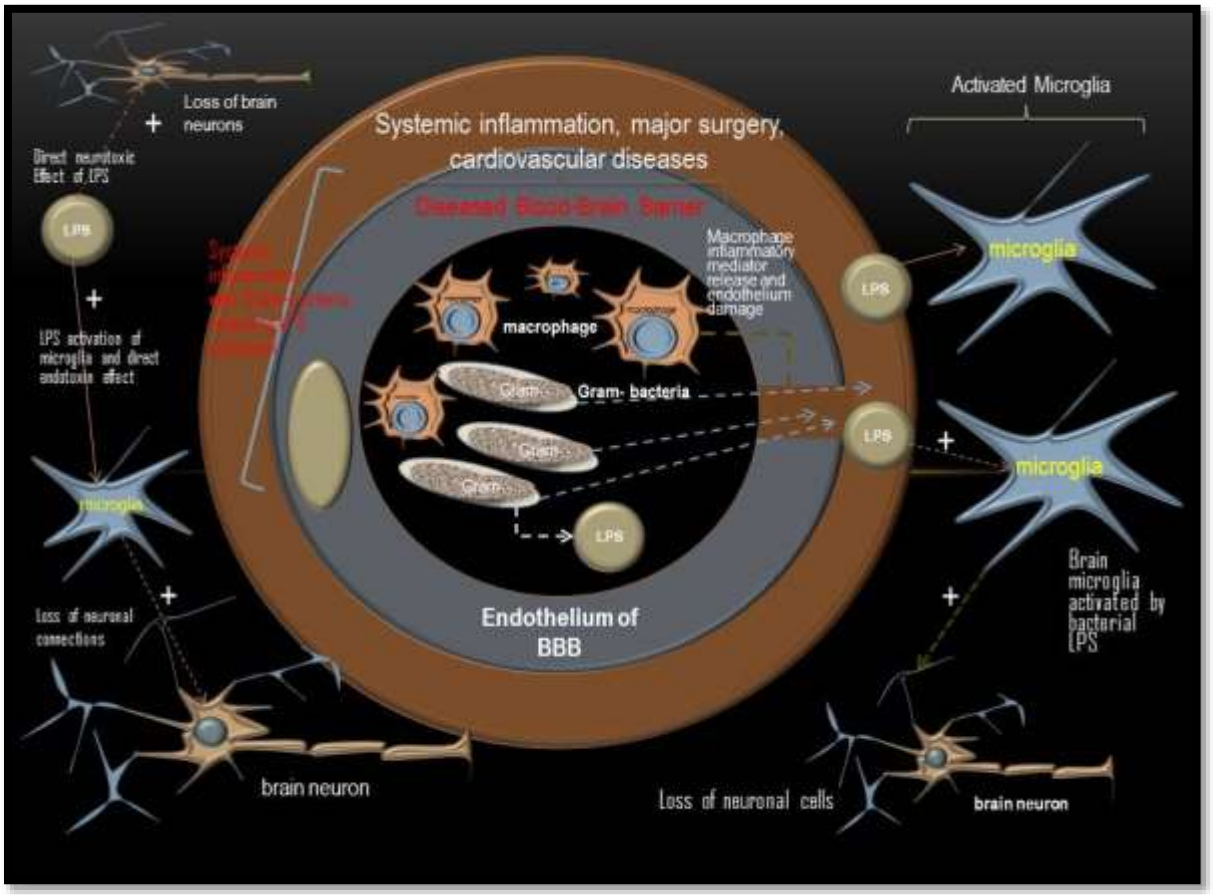

Figure 2: Pathophysiology in post-infection and post-operative Alzheimer disease. A generalise sepsis from Gram-negative bacteria release lipopolysaccharide (LPS) from their capsule which is reported to activate microglia which, then, attack brain cell with subsequent apoptosis. At the same time, LPS is an endotoxin which can attack the blood-brain-barrier (BBB) making it permeable to other inflammatory agents hence facilitating their access to the brain. A similar role is played by macrophages activated by inflammation which release inflammatory cytokines with endothelium damage of BBB.

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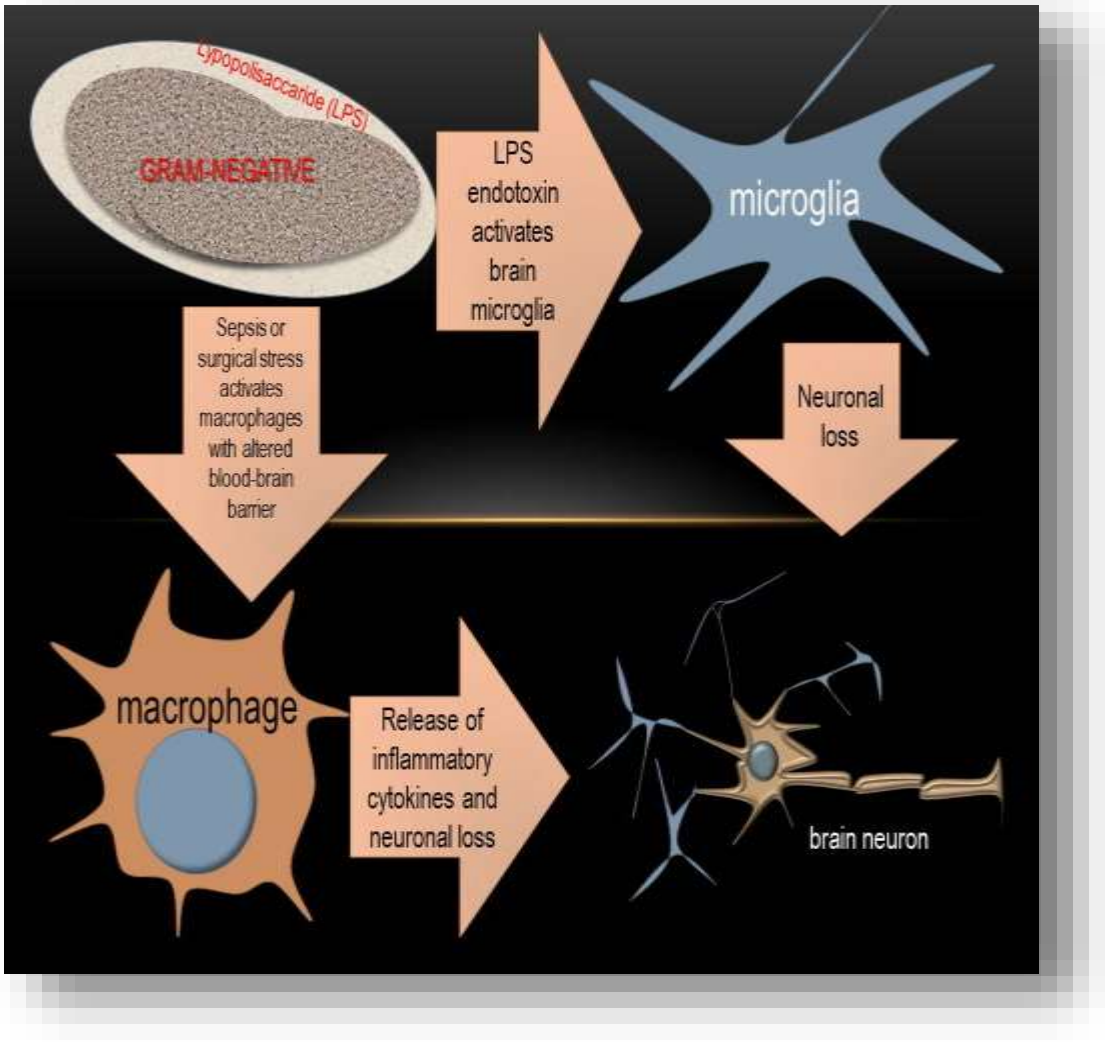

Figure 3: Cellular and inflammatory agents in post-inflammatory and post-operative dementia. Gram-negative bacteria activated by sepsis or major surgery can alter blood-brain barrier. Activated macrophages release inflammatory cytokines that alter the endothelium of the blood-brain barrier and have direct access to brain neurons. Alternatives, LPS endotoxin activates brain microglia then responsible for neuronal loss in the brain. If mesolimbic system is targeted, then research should expect effects on emotions and thoughts leading to psychosis

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