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Review

Purple urine bag syndrome and dementia. Could *E. Coli* PUBS be a risk factor for development of sporadic Alzheimer disease? A review of literature

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Introduction. PUBS (purple urinary bag syndrome) is determined by tryptophan, which is metabolized by intestinal bacteria (like *E. Coli*) and expelled into the urine. This syndrome is common in bedridden patients, usually with urinary catheterization and neurological comorbidities like dementia. Latest evidences show a possible role of *E. Coli* in Alzheimer disease.

Materials and methods. The PubMed database was evaluated according to year of pubblication (2000-2018) and following search keys: "Purple urine bag syndrome", "Gram-PUBS", "Dementia Purple urine bag syndrome", "*E. Coli* PUBS", "*E. Coli* Alzheimer disease", "Gram-Alzheimer disease". Search criteria were focused on citations describing prognosis and correlation of PUBS with neurological comorbidities and correlation between Gram - and neurophysiopathology of AD

Results. 8 references (3 case reports, 2 case series, 1 cohort study, 2 RCT) were found out of 344 citations evaluated.

Conclusions. Latest evidences show a direct link between Gram- and B-amyloid genesis. Further studies are required to clearly define if *E. Coli* PUBS might be a risk factor for development of sporadic Alzheimer disease.

Key words: PUBS, Alzheimer disease, UTI, Dementia

GENERAL CONSIDERATIONS ON PUBS: DEFINITION, ETIOLOGY, PATOGENESIS AND DIAGNOSIS

PUBS (purple urinary bag syndrome) was first time described in 1978 with a patophysiological mechanism clarified in 1988 [1]. This condition is determined by tryptophan, which is metabolized by intestinal bacteria and expelled into the urine, after the by-product indoxyl sulfate, and digested into indoxyl by sulfatases/phosphatases produced by certain bacteria including *Escherichia Coli* (*E. Coli), Proteus mirabilis, Morganella morganii (M. morganii*), *Klebsiella pneumoniae, Providencia stuartii, Providencia rettgeri and Pseudomonas aeruginosa, S. Agalactiae.* This indoxyl may convert into indigo and indirubin in the urine drainage bag and create purple discoloration [2 3].

Relevant factor for UTIs are generally impaired cognitive function, disability in daily living and urine incontinence. There are several risk factors associated with PUBS:

- female gender;
- increased dietary tryptophan;
- alkaline urine;
- constipation;
- chronic catheterisation;
- high urinary bacterial load;
- renal failure;
- use of a polyvinylchloride (PVC) plastic catheter.

Female urinary anatomy it's an already known risk factor that predisposes women to UTIs [4]. Also If patients have an increased intake of tryptophan in their diet,

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then there is an increase in the substrate for the PUBS-causing bacteria to metabolise and produce red and blue pigments. Alkalinised urine facilitates the oxidation of indoxyl sulphate to indigo and indirubin, the blue and red pigments which mix to produce the purple colour. Although alkaline urine appears a key factor in PUBS, it is not always necessary, as evidenced by a case report of PUBS in acidic urine. Severe constipation often leads to urinary retention which leaves bacteria in the urine with more time to work on their substrate (indoxyl sulphate) to produce more red and blue pigments. Gastrointestinal conditions such as obstruction, intussusception, and ileal diversions can also increase PUBS, presumably because the bacteria are allowed more time to grow and deaminate tryptophan as in constipated patients. Elderly and bedridden patients with multiple comorbidities more often require long-term indwelling catheters which increase their risk of UTIs. A greater urinary bacterial load during a UTI will obviously increase the availability of bacterial sulphatases and phosphatases which convert indoxyl sulphate to indigo and indirubin. Lastly, renal failure increases the risk of PUBS because there is impaired clearance of indoxyl sulphate meaning the urinary bacteria have more substrate to produce the red and blue pigments and therefore purple urine [5 6].

Moreover we have to focus on risking misdiagnosis, so we'll have to have to use a standard approaching to urine discoloration like using Oxford Urine Chart.

E. COLI AND ALZHEIMER'S DISEASE: ROLE OF GUT MICROBIOMA IN DEMENTIA AND NEW POSSIBLE RESEARCH FRONTIERS

Alzheimer's disease is determined by abnormal accumulation of B-protein, component of amyloid AB. This protein, formed by 40-42 aminoacids, is a metabolic derivative from APP (codified from chromosome 21) through the enzimatic action of B and g secretase. B protein has a proaggregant effect forming amyloid fibers. The state of polymerization induces, at neuronal level, the trigger of an oxidative stress resulting in neuronal apoptosis associated with mitochondrial damage [7 8]. However, this hypothesis is paradoxical: the concentrations of AB required for fibrillization and neurotoxicity are higher than its physiological concentrations. Cognitive decline in AD patients is not correlated with the levels of senile plaque formation or insoluble Abeta formation; instead it correlates with the levels of synapse loss and the levels of soluble AB. These observations suggest the existence of soluble toxic forms of AB in AD brains; these forms have recently been identified to be oligomeric assemblies of AB. At present, AD is believed to begin with synaptic dysfunction caused by soluble AB oligomers. This hypothesis termed the oligomer hypothesis, is based on the following observations: The levels of AB oligomers are high in AD brains. Exogenous AB oligomers at physiological concentrations cause synaptic and cognitive dysfunction *in vivo* and synapse loss and neuronal death *in vitro* [9 10 11].

Different studies argue the ability, by Gram – (in particular *E. Coli*), in genesis of B-amyloid fibrils therefore potential etiological motivation of AD [12 13]. Not only lipopolysaccharide or lipooligosaccharide, but also snc-RNA and both endotoxins and exotoxins can contribute to the development of neurotoxic and pro-inflammatory damage. This is determined by:

- that the GI tract microbiome are a potent source of neurotoxic species that are abundantly secreted by multiple Gram-negative bacilli in the gut (*B. Fragilis*, *E. Coli*, and others);
- that bacterial LPS are readily detectable in the neocortex and hippocampus of the AD brain, and at significantly higher abundance in AD than controls, indicating that LPS may be able to transit physiological barriers to access CNS compartments;
- that the transit of highly pro-inflammatory neurotoxins such as LPS across compromised GI tract and blood-brain barriers underscore the critical roles of cellular adhesion structures in allowing passage of noxious molecules from the GI tract into the systemic circulation and CNS;
- that extremely complex mixtures of neurotoxins may be generated by either single microbes or by combinations of bacilli that constitute the GI tract microbiome;
- that biophysical, gastrointestinal, and neurobiological barriers that may become more "leaky" with aging again underscore the important role of intact membrane barriers in moderating systemic and CNS inflammation and immune-mediated inflammatory disease;
- that bacterial complexity, neurotoxin abundance, speciation, and complexity in the CSF, blood serum or in brain tissues may be useful for the diagnosis of AD;
- and that studies on the thanatomicrobiome should be useful for a clearer understanding of the neuro- and micro-biological processes in operation over the PMI that should be useful in scientific research that utilizes post-mortem tissues in basic research, in forensic applications, in criminology and in the more accurate diagnosis of neurological disease;
- that the presence of frequent urinary infections, reality of the elderly with dementia, supported by *E. Coli*, can facilitate the deposition of amyloid by further elevation of the expression of the *Piezo channell* at the level of the hippocampus and the cortex [14-16].

MATERIALS AND METHODS

The PubMed database was evaluated according to year of pubblication (2000-2018) and the following search keys: "Purple urine bag syndrome", "Gram-PUBS", "Dementia Purple urine bag syndrome", "*E. Coli* PUBS", "*E. Coli* Alzheimer disease", "Gram-Alzheimer disease". A total of 344 articles were found. Subsequently, the real relevance to the subject of this review was assessed, thus arriving at 50 articles. At this point the following inclusion criteria were used:

- references that focus on the prognosis and correlation of PUBS with neurological/demented frameworks;
- if the sources used were focused on the correlation between Gram – and neurophysiopathology of AD.

This allowed to further select 8 references, for a total of 344 articles, divided into:

- case report: 3 references, 3 patients;
- case series: 2 references, 20 patients;
- cohort studies: 1 reference, 643 patients;
- RCT: 2 references, 125 brain.

A summary table and a PRISME diagram were obtained and listed below (Tab. I).

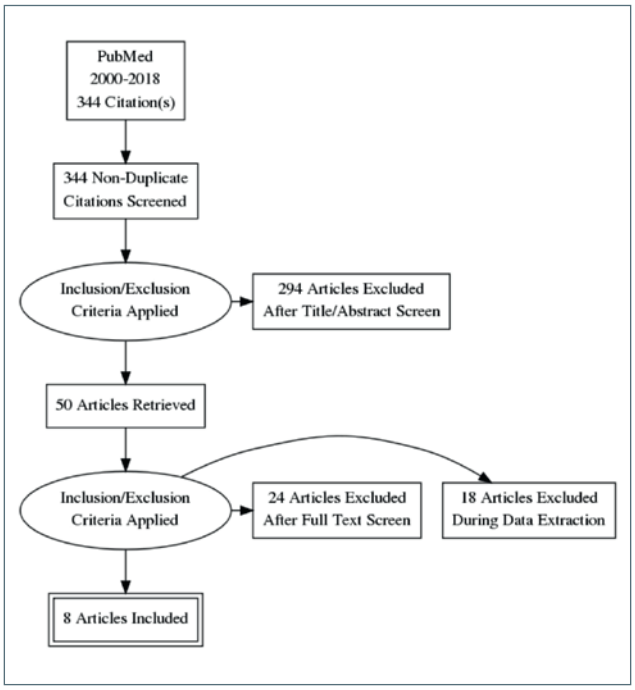

Figure 1. PRISME diagram: 8 of 344 citations evaluated were used in this article.

RESULTS

A total 344 citations on PubMed database, after reading full text or abstract were used 50 references of the database used. Analyzing total population and statical relevacy were chosen only 8 references (791 samples) (Fig. 1).

E. Coli substained UTIs are a common reality in old patients and can show themselves in PUBS (a striking clinical manifestation which can be of particular concern among the care staff) or with more common clinical features. Clearly relevant is the neurological consequences due to UTI (often caused by intestinal bacterial flora) [15-22].

CONCLUSIONS

Cognitive impairment, like urine incontinency and ADL disability, is a risk factor for UTIs development [23]. This condition represents a burdensome financial cost and reveals that they are very important in understanding length of stay and costs in older and complex patients [24]. Alzheimer dementia have a complex paophiology determined by a neuronal damage which amyloid has a central role, latest evidences show a primary role of microbiome in development of neurocognitive impairments calling: the gut-brain axis. The interaction between the host and its gut microbiome is a complex relationship whose manipulation could prove critical to preventing or treating not only various gut disorders, like irritable bowel syndrome (IBS) and ulcerative colitis (UC), but also central nervous system (CNS) disorders, such as Alzheimer's and Parkinson's diseases.

In particular about *E. Coli*, a Gram – bacterium member of gut microbiome and also causing UTIs (like PUBSs), is defined like a possible cause of amyloidogenesis [22]. This relationship could depend to LPS production from major bacterial species of the GI tract, such as the abundant Gram-negative bacilli *B. Fragilis* and *E. Coli*, secrete a remarkably complex array of pro-inflammatory neurotoxins which, when released from the confines of the healthy GE tract, are pathogenic and highly detrimental to the homeostatic function of neurons in the central nervous system (CNS) [14 16].

Like said before there's actually no evidences directly connecting *E. Coli* PUBS and Alzheimer's disease, but often this urological syndrome (like others UTIs) is commonly in old patients with cognitive impairment (like AD). So it's needed more studies assessing the relationship between PUBS and AD, this could establish PUBS like a "alarm bell" for alterations of gut microbiome probably developing in neurocognitive impairment and also further increase of disability [22-24].

Table I. Summary table of references used in this review.

Authors	Date	Study type	Details of study population	Materials and methods	Conclusions
Mondragón -Cardona A. et al., J Infect Dev Ctries	2015	Case report	71-year-old, F, catheterized, AD, bedridden, neurological sequelae	Evidence of *E. Coli, E. Faecalis, P. Mirabilis* in urinocolture	Focus on PUBS outcome in multi-morbidity patients
Eriksson I et al., International Psychogeriatrics	2011	Cohort study	643 > 85 years, F, at home. 504 with UTIs	504 UTI and almost half of them (44.8%) were diagnosed to be delirious or having had episodes of delirium during the past month. 132 of the 504 women (27.2%) were delirious or had had episodes of delirium during the past month and 39 (28.5%) of them were diagnosed to have a UTI	UTI is a common cause of delirium
Reginald A et al., J Family Med Prim Care.	2015	Case report	83 years, M, IPB, renal failure, permanent cv	Evidence of *Klebsiella pneumonia, Morganella Morganii, Enterococcus, Citrobaterdiversus* and *Pseudomonas aeruginosa* in urinoculture	Correlation with poor prognosis especially in old patients with permanent VC
Kalsi DS et al., Disease markers.	2017	Case series	10 cases of PUBS determined by various etiological factors	4 out of 10 cases of PUBS have been highlighted in patients with dementia 5 cases out of 10 PUBS supported by *E. Coli*	Correlation with already known microbiological risk factors via exposure of clinical cases
Bhattarai M et al., Case Rep Infect Dis.	2013	Case reports	An 87-year-old Caucasian female, dementia, hypertension, hyperlipidemia, and recurrent UTI	Urinocultures of *Enterococci* and multiresistant *P. aeruginosa*	PUBS can be associated with multiresistant microbes. The color change of the urine should not be left lost but investigated immediately due to risk of complications
Zhan X et al., American Academy of Neurology	2016	RCT	24 brain samples with AD 18 brain samples without	Lipopolysaccharide (LPS) and *E. Coli* K99 pili protein were evaluated by Western blots and immunocytochemistry. Human brain samples were assessed for *E. Coli* DNA followed by DNA sequencing	*E. Coli* K99 and LPS levels were greater in AD compared to control brains. LPS is in amyloid plaques and around vessels in AD brain
Lin CH et al., Clinical Interventions in Aging	2008	Case series	10 case reports. 5 with AD 60-89 years-old	Identified in the urinocoltures: *Escherichia strains, Klebsiella Pneumoniae, Providencia rettegeri and Proteus mirabilis*	Necessity to treat with more aggressiveness such patients especially if allured for bad prognosis
Cattaneo A et al., Neurobiology of Aging	2017	RCT	73 brains with AD (40 Amy+, 33 Amy -) and 10 normal brains	In both study groups have been assessed both microbiological analysis of stood samples (frequently founded GMB taxa like *Escherichia/Shigella, Pseudomonas aeruginosa, Eubacterium rectale*, and others) and the blood expression levels of cytokines (pro-inflammatory cytokines: CXCL2, CXCL10, interleukin [IL]-1B, IL-6, IL-18, IL-8, inflammasome complex (NLRP3), tumor necrosis factor-alpha [TNF-a]; anti-inflammatory cytokines: IL-4, IL-10, IL-13)	An increase in the abundance of a pro-inflammatory GMB taxon, *Escherichia/ Shigella,* and a reduction in the abundance of an anti-inflammatory taxon, *E. Rectale*, are possibly associated with a peripheral inflammatory state in patients with cognitive impairment and brain amyloidosis

Conflict of interest

The Authors declare to have no conflicts of interest.

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