

Supplement

Brain Sagging Dementia - Diagnosis, Treatment and Outcome: A Review

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eTable 1. Systematic Review Search Protocol

Sources used for the search:

Database	April 21 st 2021
MEDLINE (Ovid):	467
Embase (Ovid):	910
Cochrane Library:	19
PsycInfo (Ovid):	58
Number of references prior to duplicate deletion	1454
Number of references after duplicate deletion	983

The search was initially performed on September 30th 2019 and updated on April 21st 2021.

The search was conducted by Hilde Iren Flaatten, Medical Librarian, University of Oslo: Library of Medicine and Science. Literature searching and Evidence-Based Practice Unit

Database: Ovid MEDLINE(R) ALL

- 1 Intracranial Hypotension/ or (intracranial hypotension or intra-cranial hypotension or intracranial csf hypotension or intra-cranial csf hypotension or craniospinal hypotension).tw,kf.
- 2 exp Cerebrospinal Fluid Leak/ or ((CSF adj3 (leak* or hypovolemi* or hypovolaemi* or rhinorrhoea* or otorrhea*)) or (cerebr* adj3 (leak* or hypovolemi* or hypovolaemi* or rhinorrhoea* or otorrhea*)) or liquorr*).tw,kf.
- 3 ((low cerebro* adj2 pressure) or orthostatic headache* or postural headache*).tw,kf.
- 4 or/1-3
- 5 Dementia/ or cognition disorders/ or cognitive dysfunction/ or Neurocognitive Disorders/ or (dementia or cognit* or neurocognit* or behav* or (personal* adj2 change*)).tw,kf.
- 6 Apathy/ or Stupor/ or (apath* or disinhibition* or confusion* or disorientation* or desorientation* or stupor*).tw,kf.
- 7 memory disorders/ or exp amnesia/ or (memory or memories or amnesia).tw,kf.
- 8 communication disorders/ or language disorders/ or speech disorders/ or confusion/ or ((impair* or loss or disorder* or defect* or deficit* or dysfunction* or decline* or disturbance* or problem*) adj3 (language or speech or communication)).tw,kf.
- 9 psychology.fs. or (neuropsychological* or psychological* or mental state* or mental status).tw,kf.
- 10 or/5-9
- 11 4 and 10
- 12 ((brain adj3 sagging) or (brain adj3 sag) or (brain adj3 sagged) or (brain adj3 sink*) or (cerebr* adj3 sagging) or (cerebr* adj3 sag) or (cerebr* adj3 sagged)).tw,kf.
- 13 11 or 12
- 14 limit 13 to english language

Compressed search:

((Intracranial Hypotension/ or exp Cerebrospinal Fluid Leak/ or (intracranial hypotension or intra-cranial hypotension or intracranial csf hypotension or intra-cranial csf hypotension or craniospinal hypotension or (CSF adj3 (leak* or hypovolemi* or hypovolaemi* or rhinorrhoea* or otorrhea*)) or (cerebr* adj3 (leak* or hypovolemi* or hypovolaemi*)) or liquorrhea or (low cerebro* adj2 pressure) or orthostatic headache* or postural headache*).tw,kf.) and (Dementia/ or Cognition Disorders/ or Neurocognitive Disorders/ or Apathy/ or Stupor/ or memory disorders/ or exp amnesia/ or communication disorders/ or language disorders/ or speech disorders/ or confusion/ or

psychology.fs. or (dementia or cognit* or neurocognit* or behav* or (personal* adj2 change*) or apath* or disinhibition* or confusion* or disorientation* or desorientation* or stupor* or memory or memories or amnesia or neuropsychological* or psychological* or mental state* or mental status or ((impair* or loss or disorder* or defect* or deficit* or dysfunction* or decline* or disturbance* or problem*) adj3 (language or speech or communication))).tw,kf.)) or ((brain adj3 sagging) or (brain adj3 sag) or (brain adj3 sagged) or (brain adj3 sink*) or (cerebr* adj3 sagging) or (cerebr* adj3 sag) or (cerebr* adj3 sagged)).tw,kf.

Database: Embase Classic+Embase

- 1 intracranial hypotension/ or (intracranial hypotension or intra-cranial hypotension or intracranial csf hypotension or intra-cranial csf hypotension or craniospinal hypotension).tw,kw.
- 2 exp liquorrhea/ or ((CSF adj3 (leak* or hypovolemi* or hypovolaemi* or rhinorrhoea* or otorrhea*)) or (cerebr* adj3 (leak* or hypovolemi* or hypovolaemi* or rhinorrhoea* or otorrhea*)) or liquorr*).tw,kw.
- 3 ((low cerebro* adj2 pressure) or orthostatic headache* or postural headache*).tw,kw.
- 4 or/1-3
- 5 dementia/ or cognitive defect/ or mild cognitive impairment/ or exp confusion/ or "disorders of higher cerebral function"/ or disorientation/ or apathy/ or stupor/
- 6 behavior disorder/ or abnormal behavior/ or exp disruptive behavior/ or exp impulse control disorder/
- 7 (dementia or cognit* or neurocognit* or behav* or (personal* adj2 change*)).tw,kw.
- 8 (apath* or disinhibition* or confusion* or disorientation* or desorientation* or stupor*).tw,kw.
- 9 memory disorder/ or exp amnesia/ or (memory or memories or amnesia).tw,kw.
- 10 communication disorder/ or language disability/ or speech disorder/
- 11 ((impair* or loss or disorder* or defect* or deficit* or dysfunction* or decline* or disturbance* or problem*) adj3 (language or speech or communication)).tw,kw.
- 12 mental health/ or (neuropsychological* or psychological* or mental state* or mental status).tw,kw.
- 13 or/5-12
- 14 4 and 13
- 15 ((brain adj3 sagging) or (brain adj3 sag) or (brain adj3 sagged) or (brain adj3 sink*) or (cerebr* adj3 sagging) or (cerebr* adj3 sag) or (cerebr* adj3 sagged)).tw,kw.
- 16 14 or 15
- 17 limit 16 to conference abstract
- 18 16 not 17
- 19 limit 18 to english language

Database: Cochrane Library

<https://bit.ly/2n5DWth>

- #1 MeSH descriptor: [Intracranial Hypotension] this term only
- #2 (intracranial NEXT hypotension or intra NEXT cranial NEXT hypotension or intracranial NEXT csf NEXT hypotension or intra NEXT cranial NEXT csf NEXT hypotension):ti,ab,kw OR (or craniospinal NEXT hypotension):ti,ab,kw (Word variations have been searched)
- #3 MeSH descriptor: [Cerebrospinal Fluid Leak] explode all trees

#4 (CSF NEAR/2 (leak* or hypovolemi* or hypovolaemi* or rhinorrhoea* or otorrhea*)):ti,ab,kw
OR (cerebr* NEAR/2 (leak* or hypovolemi* or hypovolaemi* or rhinorrhoea* or otorrhea*)):ti,ab,kw
OR (liquorr*):ti,ab,kw (Word variations have been searched)

#5 (low cerebro* NEAR/1 pressure):ti,ab,kw OR (orthostatic NEXT headache*):ti,ab,kw OR
(postural NEXT headache*):ti,ab,kw (Word variations have been searched)

#6 {OR #1-#5}

#7 MeSH descriptor: [Dementia] this term only

#8 MeSH descriptor: [Cognition Disorders] this term only

#9 MeSH descriptor: [Cognitive Dysfunction] this term only

#10 MeSH descriptor: [Neurocognitive Disorders] this term only

#11 (dementia or cognit* or neurocognit* or behav*):ti,ab,kw OR (personal* NEAR/1
change*):ti,ab,kw (Word variations have been searched)

#12 MeSH descriptor: [Apathy] this term only

#13 MeSH descriptor: [Stupor] this term only

#14 (apath* or disinhibition* or confusion* or disorientation* or desorientation* or
stupor*):ti,ab,kw (Word variations have been searched)

#15 MeSH descriptor: [Memory Disorders] this term only

#16 MeSH descriptor: [Amnesia] explode all trees

#17 (memory or memories or amnesia):ti,ab,kw (Word variations have been searched)

#18 MeSH descriptor: [Communication Disorders] this term only

#19 MeSH descriptor: [Language Disorders] this term only

#20 MeSH descriptor: [Speech Disorders] this term only

#21 MeSH descriptor: [Confusion] this term only

#22 ((impair* or loss or disorder* or defect* or deficit* or dysfunction* or decline* or
disturbance* or problem*) NEAR/2 (language or speech or communication)):ti,ab,kw (Word
variations have been searched)

#23 MeSH descriptor: [] explode all trees and with qualifier(s): [psychology - PX]

#24 (neuropsychological* or psychological* or (mental NEXT state*) or (mental NEXT
status)):ti,ab,kw (Word variations have been searched)

#25 {OR #7-#24}

#26 #6 AND #25

#27 ((brain NEAR/2 sagging) or (brain NEAR/2 sag) or (brain NEAR/2 sagged) or (brain NEAR/2
sink*) or (cerebr* NEAR/2 sagging) or (cerebr* NEAR/2 sag) or (cerebr* NEAR/2 sagged)):ti,ab,kw
(Word variations have been searched)

#28 #26 OR #27

Database: APA PsycInfo 1806 to April Week 2 2021

- 1 (intracranial hypotension or intra-cranial hypotension or intracranial csf hypotension or intra-
cranial csf hypotension or craniospinal hypotension).mp.
- 2 ((CSF adj3 (leak* or hypovolemi* or hypovolaemi* or rhinorrhoea* or otorrhea*)) or (cerebr*
adj3 (leak* or hypovolemi* or hypovolaemi* or rhinorrhoea* or otorrhea*)) or liquorr*).mp.
- 3 ((low cerebro* adj2 pressure) or orthostatic headache* or postural headache*).mp.
- 4 or/1-3
- 5 (dementia or cognit* or neurocognit* or behav* or (personal* adj2 change*)).mp.
- 6 (apath* or disinhibition* or confusion* or disorientation* or desorientation* or stupor*).mp.
- 7 (neuropsychological* or psychological* or mental state* or mental status).mp.
- 8 (memory or memories or amnesia).mp.
- 9 ((impair* or loss or disorder* or defect* or deficit* or dysfunction* or decline* or disturbance*
or problem*) adj3 (language or speech or communication)).mp.

- 10 or/5-9
- 11 4 and 10
- 12 ((brain adj3 sagging) or (brain adj3 sag) or (brain adj3 sagged) or (brain adj3 sink*) or (cerebr* adj3 sagging) or (cerebr* adj3 sag) or (cerebr* adj3 sagged)).mp.
- 13 11 or 12
- 14 limit 13 to english language

eTable 2. Oxford Centre of Evidence Based Medicine (OCEBM)

Levels of evidence	Study reference
1	None
2	None
3	None
4	1-4
5	5-29

Explanation of levels:

1. Systematic review with meta-analysis of RCTs
2. RCT or observational study of high quality
3. Non-randomized follow-up/observational study
4. Case series or case-control studies
5. Mechanism-based reasoning (expert opinion, case report, animal or laboratory studies)

OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. Accessed February 26, 2021. <http://www.cebm.net/index.aspx?o=5653>*

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

eTable 3. References

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eTable 4: Summary of the Case Reports Included in the Review

Title, Author, Year	Gender, Age	Presenting symptoms, duration	Other symptoms	Cognitive/ behavioral changes	Imaging	Leak identified/location	Modes of treatment	Response to treatment
Pleasure, S. J. 1998 ²⁴	Male, 51	Headache, 4m	Gradual onset of somnolence, incontinence of urine and stool, unsteady gait	Inattentiveness, poor anterograde memory.	PME, BS, SDE	Yes (Th4)	EBP (x3), intrathecal saline infusion, EBP (Th4), Surgical repair	Yes
Hong, M. 2002 ⁵	Male, 66	Personality and behavioral changes, memory loss, and chronic daily headache, 18m		Mild declines in overall intellectual ability and memory. Socially and sexually inappropriate, inactive. MMSE 21/30	PME, BS, SDE	No	Steroids	Yes
Peng, P.W. 2004 ²⁵	Female, 50	Headache, 2m	Sensorineural hearing loss, gait disturbance	Short-term memory loss, MMSE 26/30	PME, BS, SDE	No	EBP	Yes
Weisfelt, M. 2004 ³⁸	Male, 51	Headache, 6w	Ataxic gait, hypersomnolence	Cognitive decline, fluctuating GCS	PME, BS, SDE	Yes, Th4	Saline infusion with lumbar drain, EBP at Th4*	Yes
Binder, D.K. 2005 ⁴⁶	Female, 55	Headache, 6w		Aural fullness, memory difficulties, and disorientation	PME, BS	Yes, Th2-Th3	EBP, median sternotomy and discectomy with primary dural repair*	Yes
Tsai, P.H. 2005 ³¹	Female, 55	Headache, 43d	Rhinorrhea	intermittent outbursts of bizarre speech, loquacious. MMSE 24	PME, BS, SDE	Yes (Th7-Th9)	EBP (x2)*	Yes
Mokri, B. 2006 ²⁷	Male, 59	Headache, memory complaints, 4y	Choreiform movements, dysarthria, and dysphagia	Difficulties with concentration, attention and learning	PME, BS	Yes, Th9-Th10	Surgical decompression and repair, EBP (cervical)*	Yes
Walker, L. 2008 ⁷	Male, mid-50s	Headache, 8w	Problems with balance, marked disinhibition	Juvenile humor, increased anger/aggression, bizarre behavior, socially and sexually inappropriate, MMSE 29/30	PME, BS, SDE	No	EBP, Steroids*	Yes
Agarwal, P. 2009 ⁵²	Male, 50	Headache, 2m	Urinary incontinence, extensor plantar reflexes	Dull and apathetic	PME, BS, SDE	No	EBP (x2)*	Yes

Devine, M. J. 2009 ²²	Male, 46	Aural fullness and muffled hearing, 9m	Headache, unsteady gait, recurrent hiccups, urinary incontinence	Antegrade amnesia, disoriented, MMSE 20/30	PME, BS, SDE	No	Steroids	Yes
Sayao, A. L. 2009 ⁸	Male, 58	Odd behavior, few m	Headache, ataxic gait, mild dysarthria	Bizarre behavior, neologism, confabulation, echolalia, disoriented, memory loss	PME, BS, SDE	Yes, C2	Intrathecal saline infusion, EBP (C2)*	Yes
Khan, J. A. 2010 ³²	Male, 40	Headache, fatigue, and personality changes, 4y	Restlessness, dysarthria, and brisk upper limb reflexes.	Stereotypical motor perseveration, blunted affect, sexually inappropriate	BS	No	EBP (x3)	Temporary effect
Vetrugno, R. 2011 ¹⁹	Female, 60	Decreased voluntary and purposeful behaviors, 2y		Mild deficits in word learning and visuo-spatial memory	BS	No	EBP	Yes
Mokri, B. 2014 ²⁸	Male 59	Headache, cognitive difficulties, choreiform movements, abnormal gait, dysarthria, and dysphagia		Difficulties with attention, concentration, learning, and memory.	PME, BS	Yes, Th9-Th10/cervicothoracic level	Surgical repair, EBP (cervical)*	Yes (recurrence after 5 years)
Mokri, B. 2014 ²⁸	Female 60	Headache, gait disturbance, abnormal movement of the face, difficulties with memory, 1y	Choreiform movements of face, trunk, and limbs.	Mild cognitive difficulties but substantial deficits in recall	PME, BS	Yes, lumbosacral	Surgical repair, EBP*	Yes
Slattery, C. F. 2015 ³³	Male 71 (debut at 65)	Headache, 6y	Cough	Forgetfulness, behavioral change, vocalizations	PME, BS	–	Trauma (auto-blood patch)	Yes
Batra, A. 2015 ⁵³	Male 50	Headache, confusion, 10w		Disoriented for time, psychomotor slowing, abulia, depressed mood	PME, BS, SDE	No	EBP	Yes
Mostofi, E. 2016 ³⁵	Male, 46	Hypersomnolence, mild non-postural headache, dysphagia for liquids, 2y	Fingertip paresthesia, repeated urge to bend forward and squeeze his abdomen	Sexual assault, reckless driving, drug abuse, hyperphagia, apathy, MMSE 27/30	PME, BS	No	EBP, surgical repair, EBP plus steroids*	Yes
Kumar, N. 2016 ³⁹	Male, 58	Headache, 2y	Imbalance, dysphagia	Cognitive difficulties, hypersomnolence	PME, BS	No	EBP (x5), surgical repair–Th2-Th3 nerve root ligation*	Yes

Kearney, S. 2017 ²¹	Male, 38	Personality change, 2y	Dysarthria, impaired swallowing, mild ataxia	Neglect of personal appearance and hygiene, paroxysmal stereotyped posturing, hypoactive-hypoalet behavioral syndrome	BS	No	EBP (x3)	Temporary effect
Mulroy, E. 2017 ³⁴	Male, 42	Headache (non-postural), hiccups, behavioral change, 6m	Choreoathetosis (orofacial, tongue, and limb)	Impulsivity, disinhibition, sexually inappropriate	BS	No	EBP (Th4)	No
Staudt, M. D. 2018 ²⁶	Male, 55	Neck pain, 2y	Headache, fatigue, somnolence	Cognitive impairment and complete loss of short-term memory, MMSE 25/30	PME, BS	No	EBP (x2), Surgical repair (thoracic cyst), fibrin glue injection, multilevel large volume EBP*	Yes
Kent, L., 2019 ²⁹	Male, 55	Headache, 2y	Dysphagia, dysarthria, apathic	Bizarre behavior, overeating, socially inappropriate, distractible, lacking insight	PME, BS	No	EBP (iatrogenic after lumbar puncture)	Yes
Gupta, H. V. 2020 ³⁶	Female, 65	Cognitive decline and personality change, headache (non-postural), 1y	Parkinsonism; right hand tremor slowness of gait and intermittent bladder/bowel incontinence. Daytime hypersomnolence.	Repeating herself, short-term memory loss, apathy, disinhibited behavior	PME, BS	Yes, Th9-Th10 (on DSM)	Surgical ligation of CSF venous fistula	Yes
Mandal, A. K.J. 2020 ³⁷	Male, 63	Headache, 2y	Imbalance, daytime hypersomnolence, episodes of dysphagia	Short-term memory loss, Social disinhibition, unacceptable behavior and manner, impulsive actions.	PME, BS	Yes, Th6-Th9 (on DSM)	EBP x 2 (thoracolumbar), surgical ligation of CSF venous fistula*	Yes
Ortega-Porcayo, L. A. 2020 ³⁰	Male, 72 (debut at 56)	Headache, 16 y	Hypersomnolence, sleep apnea, urinary urgency, neck pain, tremor, ataxia, dysarthria, dysphagia.	Memory impairment, disinhibited behavior, inattention, impaired judgments, bradyopsychia, bradylalia, hand and oral automatism.	PME, BS	Yes, Th6-Th7	Steroids, surgical ligation of CSF venous fistula*	Yes

BS; brain sagging, PME; pachymeningeal enhancement, SDE; subdural effusion, EBP; epidural blood patch (lumbar level if not otherwise specified), w; weeks, m; months, y; years; C; cervical, Th; thoracic, CSF; cerebrospinal fluid, MMSE; Mini Mental State Examination, DSM; digital subtraction myelogram, GCS; Glasgow Coma Scale

* : final treatment that resulted in resolution of symptoms.