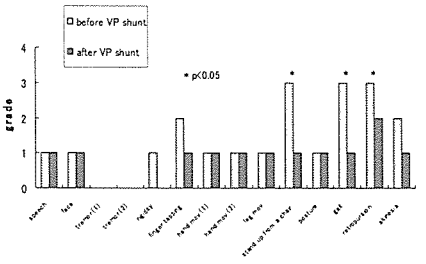
UPDRS in iNPH (average grading scores in 9 cases)



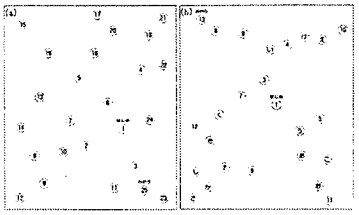
Motor sections in UPDRS

Arising, Gait and Postural stability: improved significantly
Rigidity, Finger taps and Bradykinesia: improved

Neuropsychometric tests of iNPH guidelines

1) FAB; The Fab: A frontal assessment battery at bedside
Dubois B et al. Neurology 55: 1621, 2000
made up of 6 subsections (possible total = 18 points), evaluated by interview

2) TMT; Trail Making Test and visual search
Ehrenstein WH et al. Arch Psychiatr Nervenkr 231: 333, 1982



TMT-A TMT-B

Clinical study using iNPH guidelines

Materials and methods

1) We studied 17 patients with definite iNPH showing excellent improvement of their signs and symptoms after CSF shunt operation (Clinical Guideline for iNPH by Ishikawa, M. et al. Neuro. Med. Chir. 2004).

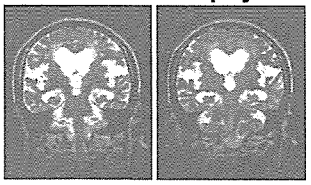
2) Parkinsonism were diagnosed if the patients showed at least two of four of the following symptoms: gait disturbance, rigidity, akinesia and resting tremor (Rampello L. 2005, Demirkiran M et al. 2001, Mizuno Y. 1997).

Clinical and Neurological Features in 18 Cases of definite iNPH

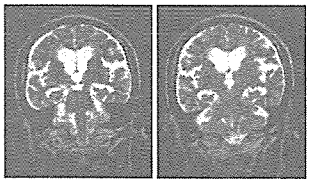
Patients		Clinical Features				Nueroradiological Features			
	Age/Sex	GD	Pa	Dem	CVD	nCHFHC	dSF	PVL	RLE
1	71M	+	+	−	+	+	+	+	+
2	82M	+	+	−	−	+	+	+	+
3	76M	+	−	−	−	+	+	+	+
4	76M	+	+	+	+	+	+	+	+
5	78M	+	+	−	+	+	+	+	−
*6	88F	+	+	+	−	+	+	+	+
7	81M	+	+	+	−	+	+	+	−
8	75F	+	−	−	−	+	+	+	+
9	77M	+	+	+	−	+	+	+	+
10	74M	+	+	+	+	+	+	+	+
11	76F	+	+	+	−	+	+	−	
12	78M	+	+	+	−	+	+	+	+
13	79M	+	+	+	−	+	+	+	+
14	75F	+	+	+	−	+	+	+	+
15	72M	+	+	−	−	+	+	+	+
16	78M	+	+	+	+	+	+	+	+
17	65M	+	+	+	−	+	+	+	+
	76.5	17(100)	15(88)	11(65)	5(29%)	17(100)	17(100)	16(94)	15(88%)
BD	70F	+	+	+	+	+	−	+	−

GD: gait disturbance, Pa: parkinsonism, Dem: dementia, CVD: history of CVD
nCSFHC: narrow CSF space at the high convexity, dSF: dilated Sylvian fissure, PVL: periventricular lucency
RLE: reversible leukoencephalopathy, * bed-ridden, akinetic mutism

TUG and neuropsychometric tests

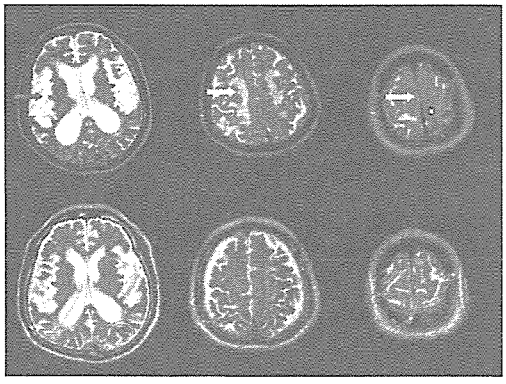


Before VP shunt
TUG: 17sec
FAB: 5/18
MMSE: 20/30
TMT: 4min 17sec



After VP shunt
TUG: 11sec
FAB: 11/18
MMSE: 25/30
TMT: 1min 53sec

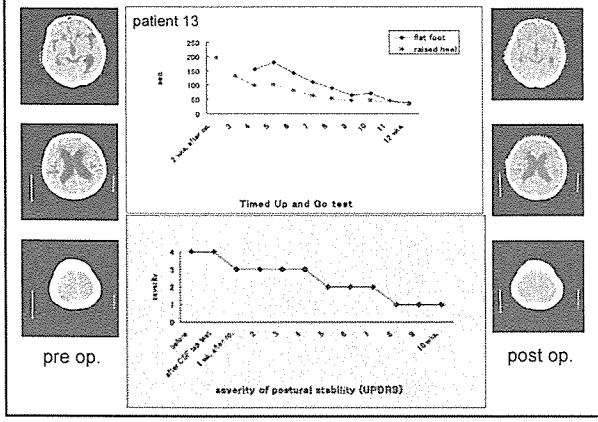
Patient 2 82 yrs male

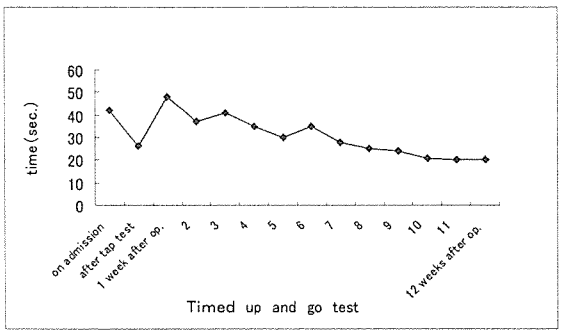


patient 6
88 yrs
female

NPH is a treatable dementia and reversible LE
upper: before VP shunt lower: after VP shunt

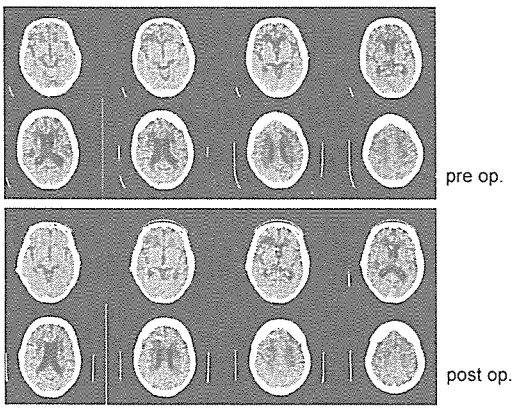
Improvement of CT abnormalities, TUG and UPDRS after operation





TUG in BD associated with iNPH

CT scans in BD associated with iNPH



Clinical and neuroradiological characteristics in 18 patients

patient no./ age, y/sex	Clinical Features	History	CT/MRI	RLE	JNPHGSR-G, C, U (pre/post-op)	UPDRSMS (pre/post-op)	TUG (pre/post-op)	MMSE-HDSR* (pre/post-op)
1/71/M	G, P	HT, CVD	nH, dS, PLH	yes	3/2, 2/1, 1/0	13/9	24/15	22/25
2/82/M	G, P	None	nH, dS, PLH	yes	3/2, 2/1, 1/0	16/6	17/11	20/25
3/76/M	G, I	HT	nH, dS, PLH	yes	3/1, 2/1, 2/1	23/10	21/15	15/22
4/76/M	G, D, I, P	CVD	nH, dS, PLH	yes	3/2, 3/2, 3/2	not done	31/17	20/22
5/78/M	G, I, P	CVD	nH, dS, PLH	yes	4/3, 2/1, 4/2	not done	not done	not done
6/88/F	G, D, I, P	None	nH, dS, PLH	yes	4/4, 4/4, 4/4	not done	not done	not done
7/81/M	G, D, I, P	HT	nH, dS, PLH	no	3/2, 3/2, 2/1	20/18	16/12	23/28
8/75/F	G	None	nH, dS, PLH	yes	3/1, 2/1, 0/0	3/1	17/14	23/26
9/77/M	G, D, I, P	None	nH, dS, PLH	yes	2/1, 3/3, 3/1	21/14	not done	14/15
10/74/M	G, D, I, P	CVD	nH, dS, PLH	yes	3/2, 3/2, 3/1	21/7	not done	6/14*
11/76/F	G, D, I, P	None	nH, dS	-	3/2, 3/2, 3/1	16/8	not done	not done
12/78/M	G, D, I, P	HT	nH, dS, PLH	yes	3/2, 3/3, 3/3	25/17	not done	9/12*
13/79/M	G, D, P	HT	nH, dS, PLH	yes	2/1, 3/3, 0/0	11/3	not done	10/11*
14/75/F	G, D, P	HT	nH, dS, PLH	yes	2/1, 3/2, 1/0	13/9	not done	9/13*
15/72/M	G, P	HT	nH, dS, PLH	yes	2/1, 2/2, 1/1	14/8	not done	18/23*
16/78/M	G, D, I, P	HT, CVD	nH, dS, PLH	yes	4/2, 3/2, 3/0	27/13	impossible/42	10/16
17/66/M	G, D, I, P	None	nH, dS, PLH	yes	4/2, 3/2, 3/3	28/20	impossible/125	3/5
18/70/F	G, D, I, P	HT, CVD	nH, PLH	no	3/2, 3/3, 4/4	28/22	42/37	6/6

1-17 ; iNPH 18 ; BD associated with NPH

Summary of evaluation criteria before and after shunt operation

	pre-op Median(Range)	post-op Median(Range)	p Values
JNPHGSR (n=17)			
gait disturbance	3 (2-4)	2 (1-4)	0.001
cognitive disturbance	3 (2-4)	2 (1-4)	<0.001
urinary disturbance	3 (0-4)	1 (0-4)	0.003
MMSE (n=9)	20 (3-23)	22 (5-28)	0.008
TUG (n=6)	19 (17-31)	14.5 (11-17)	0.027
UPDRS-Motor Score (n=14)	18 (3-28)	9 (1-20)	0.001
UPDRS-MS Categories (n=14)			
speech	1 (0-2)	0 (0-2)	0.059
facial expression	1 (0-2)	0 (0-2)	0.063
tremor at rest	0 (0-2)	0 (0-1)	0.046
action or postural tremor	0 (0-2)	0 (0-1)	0.083
rigidity	1 (0-2)	0 (0-2)	0.034
finger taps	2 (0-2)	1 (0-2)	0.025
hand movements	1 (0-2)	1 (0-2)	0.102
rapid alternating movements	1 (0-2)	1 (0-2)	0.257
leg agility	1 (0-2)	1 (0-2)	0.157
rising from chair	3 (0-4)	1 (0-3)	0.003
posture	1 (1-2)	1 (1)	0.046
gait	2 (1-4)	1 (1-2)	0.001
postural stability	2 (1-4)	1 (0-2)	0.003
body bradykinesia	2 (1-3)	1 (1-2)	0.014

Clinical study using iNPH guidelines

Results

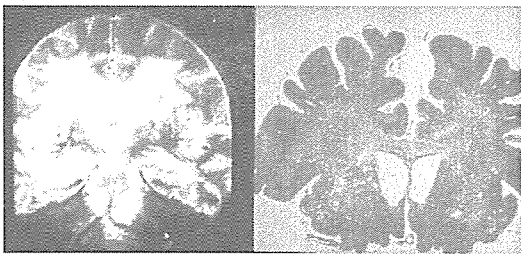
1) All patients showed specific MRI findings of both narrowing CSF space at high convexity and a diffusely dilated Sylvian fissure. These findings almost disappeared after shunt surgery. In 15 out of 16 patients the periventricular white matter lucencies or hyperintensities also showed improvement.
2) All patients showed gait disturbances and these symptoms, especially dysequilibrium, improved after the operation.
3) Patients also had more frequent parkinsonian symptoms at the onset (88%) and relatively rare signs of both cerebrovascular diseases (28%) and mental deterioration (65%).

Relationship between BD and iNPH

1) BD is a main family member of vascular dementia having distinct pathomorphology of hypertensive small artery disease.
2) On the contrary, iNPH belongs to the family of hydrocephalus with definite clinicoradiological diagnostic criteria.
3) Biopsy specimens from shunt operations were reported to often show ischemic white matter changes and Alzheimer pathology.

Diagnostic criteria of BD (Bennett et al. 1990)

1) BD is characterized by a combination of diffuse white matter lesions and a scattering of lacunar infarcts.
2) BD patients have dementia, hypertension and/or other vascular risk factors and subcortical dysfunctions such as parkinsonism.



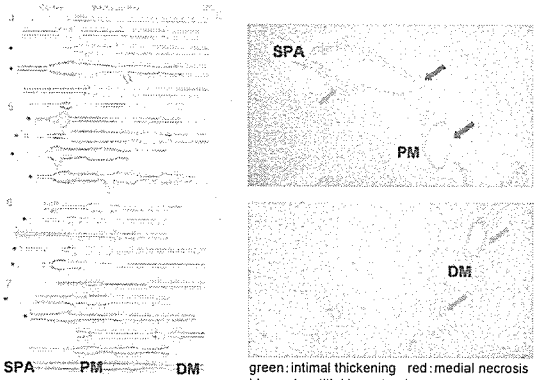
MRI T2-Weighted Image　　Brain Pathology (H&E)

Vascular mechanism and clinical syndromes in three subtypes of vascular dementias

Vascular Mechanisms	Clinical Syndromes
Cortical Vascular Dementia or Multi-infarct Dementia	
large vessel disease	bed-ridden
atherothrombotic occlusion	severe apoplexy
cardioembolic occlusion	brain attack
Subcortical Vascular Dementia or Small Vessel Dementia	
small vessel disease	Binswanger's disease
dilatative arteriopathy	vascular parkinsonism
hypoperfusion	lacunar dementia
Strategic Single Infarct Dementia	
branch atheromatous disease	amnestic syndrome
small vessel disease	(hippocampal and anterior thalamic lesions etc.)

Erkinjuntti T et al. 2002 revised

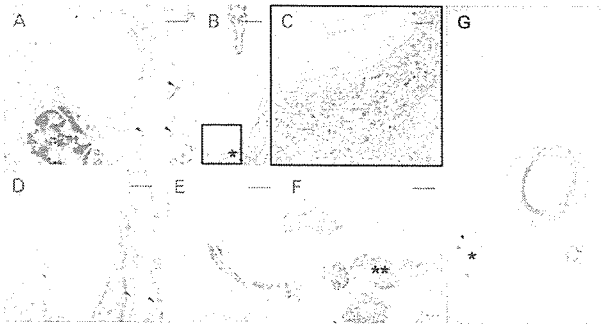
Subpial and medullary arterial lesions in BD/SVD brains



Tanoi and Okeda et al. 2000

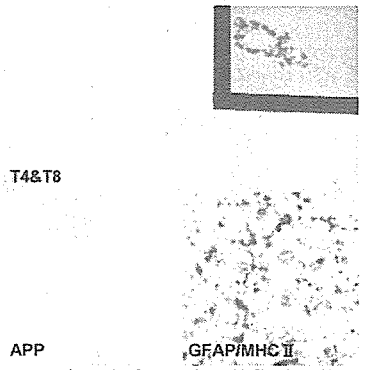
green: intimal thickening　red: medial necrosis
blue: adventitial hypertrophy

Electron immunohistochemistry of arteriolar and capillary lesions in BD/SVD brains. (Lin et al. 2000)

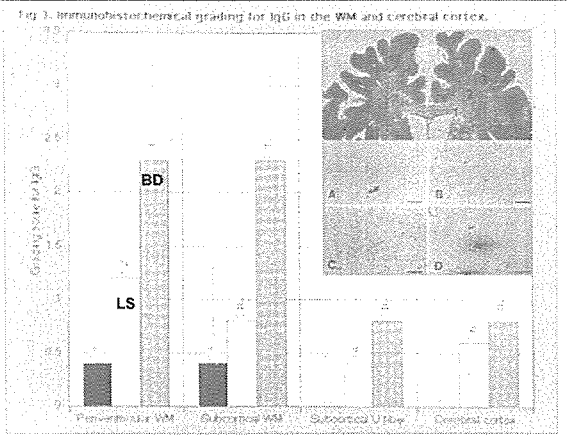


A·B·C and G: collagen type I　D: collagen type Ⅳ　E·F: SM actin
*capillary collagenosis (A~C)　**smooth muscle hypertrophy (F, E: control)

Brain pathology in BD/SVD (Akiguchi et al 1997,1999)



upper figures: perivascular & parenchymal infiltration of lymphocytes
lower left: axonal damage in WML
lower right: activated microglia (purple) & astrocyte (brown)



BBB dysfunction in BD/SVD(Akiguchi et al. 1998)

Gait Disorders and Parkinsonism in the Elderly

1) PD and parkinsonism: magnetic gait (Denny-Brown)、
gait apraxia、frozen gait、
isolated gait ignition failure (Atchison)、
primary progressive freezing gait (Achiron)

2) iNPH: gait disorder in late-life hydrocephalus (Fisher CM)
shunt-responsive parkinsonism

3) BD / vascular parkinsonism: marche a petit pas、
vascular parkinsonism

Higher level gait disorders in the elderly

1) Nutt JG & Marsden CD (Neurology 1993)
cautious gait
subcortical disequilibrium
frontal disequilibrium
isolated gait ignition failure
frontal gait disorder
2) Fisher CM (Neurology 1994)
over-65 gait disorders
over-65 symptomatic NPH gait
over-65 gait disorder of undetermined nature
Binswanger's disease
3) Liston R (Age and Ageing 2003)
ignition apraxia
equilibrium apraxia
mixed gait apraxia

Classification of vascular higher level gait disorders

Table 1. Classification of vascular HLGDs

Type of apraxia	General features	Gait disorder with normal cues	Gait disorder with stationary cues	Site of lesion
Ignition	Gait ignition failure, shuffling, freezing	Yes	Yes	SMA, GB or connections
Equilibrium	Poor balance and falls	No	No	PMA or connections
Mixed gait	Gait ignition failure, shuffling, freezing, poor balance and falls	Yes	Yes	SMA, BG or connections and PMA or connections

Liston R et al. Age and Ageing 2003

Gait disorders in iNPH fall under the mixed gait apraxia of Liston's classification. Dyseqilibrium of iNPH patients clearly Improved after shunt operation, however, gait ignition failure and hypokinesia did not improved significantly in our study.

The fourth sign in iNPH: parkinsonian syndrome

1) parkinsonism*
68% of iNPH patients showed movement disorders (parkinsonism: 11%) Krauss JK et al. 1997
88% of definite iNPH showed parkinsonism Akiguchi I et al. 2006
2) akinetic mutism#
akinetic mutism and parkinsonism appeared in obstructive hydrocephalus Berger L et al. 1985
three patients with iNPH showed treatable coma disorder with shunt troubles Lindqvist G et al. 1993

* Nigro-striatal DA pathway is injured by hydrocephalus

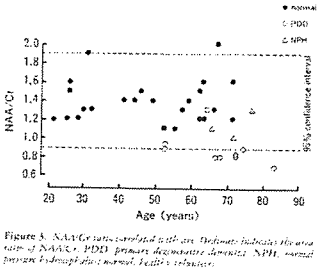
\# Meso-limbic DA pathway and the ascending reticular activating system are also injured in some cases with severe and longstanding iNPH as well as cases with aquaductal stenosis. In such cases, the pressure load to the midbrain and the floor of the third ventricle may be severe.

Reversible LE and axonal damage in iNPH

1) There is no clear description of the relationship between reversible leukoencephalopathy (rLE) and iNPH. We reported a high incidence of rLE and parkinsonism associated with definite iNPH.

2) We are now studying the role of neuroaxonal damage of the periventricular white matter and the basal ganglia in iNPH patients using N-acetylaspartate MR spectroscopy.

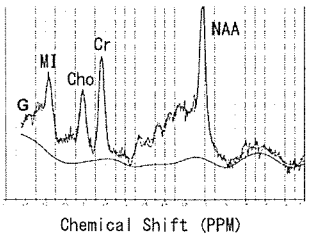
Proton Magnetic Resonance Spectroscopy with Dementia



Shiino et al.
Surg Neurol
1993

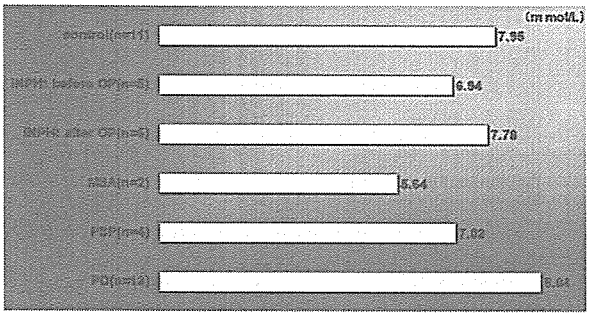
Major Intracranial Metabolites Measured by ^{1}HMRS

(1) N-acetylaspartate (NAA)
(2) Glutamate-glutamine complex
(3) Cr compounds (Cr)
(4) Choline compounds (Cho)
(5) Myo-inositol (MI)



neuroaxonal damage (1) ↓ ↓ (3) (4) ↓ AD, BD
Astrocytosis & demyelination (5) ↑ ↑, (4) ↑ → Alexander dis.

Comparison of basal ganglia NAA concentrations in various parkinsonism and iNPH before and after shunt operation



Yagi H, Akiguchi I et al. 2006

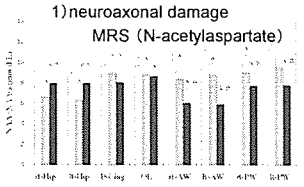
Basal ganglia NAA concentrations in iNPH and various parkinsonism

1) In iNPH preoperative neuroaxonal hypoactivity in basal ganglia seems to recover to base line levels of the normal control (reversible neuroaxonal damage!).

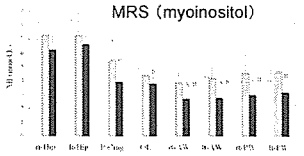
2) In Parkinson disease neuroaxonal hyperactivity of the basal ganglia is thought to occur, while in PSP and MSA it is thought to be hypoactive.

NAA and myoinositol concentrations in BD

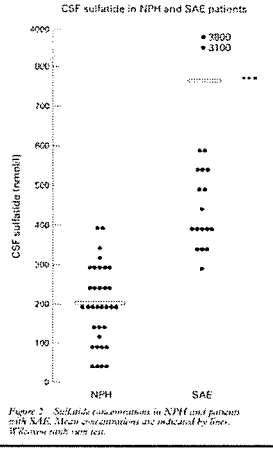
1) neuroaxonal damage
MRS (N-acetylaspartate)



2) astrocytosis and demyelination
MRS (myoinositol)



white: control
gray: AD
black: BD



1) CSF sulfatide: NPH→ BD ↑

CSF sulfatide distinguishes between normal pressure hydrocephalus and subcortical arteriosclerotic encephalopathy

2) Meningeal derived CSF protein (beta-trace): NPH ↓

3) Aβ42: NPH ↓ AD ↓
total tau: NPH→ AD ↑

Immunoreactivities of amyloid β peptide$_{1-42}$ and total τ protein in lumbar cerebro-spinal fluid of patients with normal pressure hydrocephalus

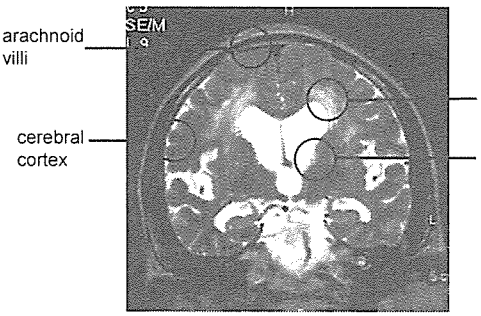
Neuropathological reports in iNPH

1) Etiopathology in arachnoid villi and meninges;
only inflammatory reaction and fibrosis of the meninges, choroid plexus and/or arachonoid villi were reported (Jellinger K 1976, Massicolle EM 1999)

2) CVD/BD pathology;
possible relation to NPH and BD (Koto A 1978)
high incidence of white matter lesions (15% or more), vascular risk factors and arteriosclerotic diseases (Akai K 1987, Krauss JK 1996, Bech AR 1997)

3) AD pathology
22~48%(Bech AR 1997,1999); 24%(Del Bigio MR 1997); 32%(Savolainen S 2000); 20%(Golomb J 2000); 6%(CERAD diagnosis of definite AD:Golomb J 2000)

Suspected CSF absorption sites in iNPH brain (Ishikawa M)

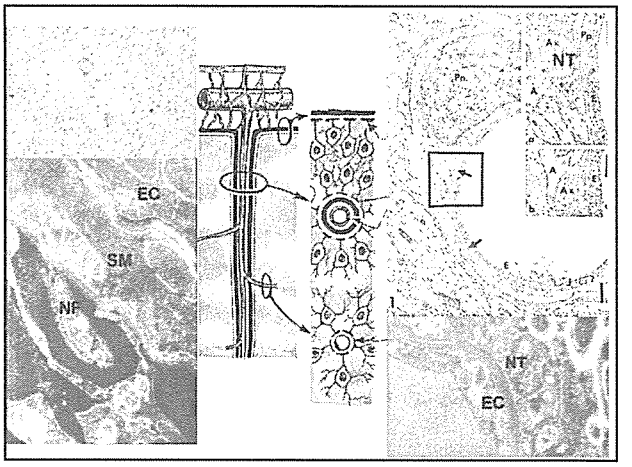


1) Pacchionian body (bulk flow theory)
2) capillary (subarachnoid/extracellular space)
3) arterioles (Virchow-Robin space)

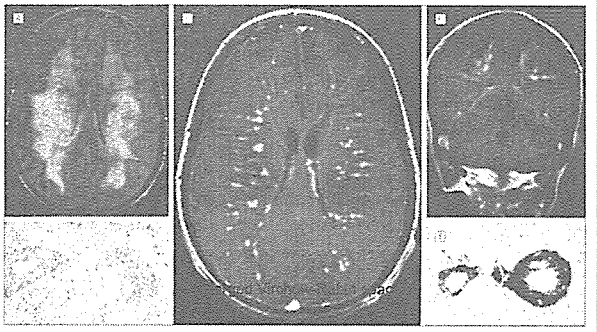
Radiological assessment of hydrocephalus; new theories and implications for therapy

Greitz D Neurosurg Rev 2004

Chronic hydrocephalus consists of two subtypes, communicating hydrocephalus and chronic obstructive hydrocephalus. The associated malabsorption of CSF is not involved as a causative factor in chronic hydrocephalus (the CSF bulk flow theory). Instead, it is suggested that increased pulse pressure in the brain capillaries maintains the ventricular enlargement in chronic hydrocephalus (restricted arterial pulsation hydrocephalus or increased capillary pulsation hydrocephalus).

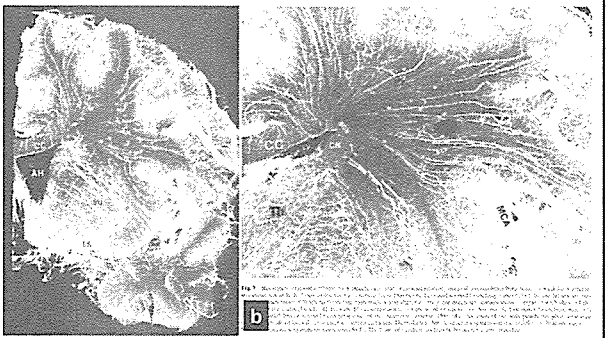


Atypical appearance of a primary CNS lymphoma



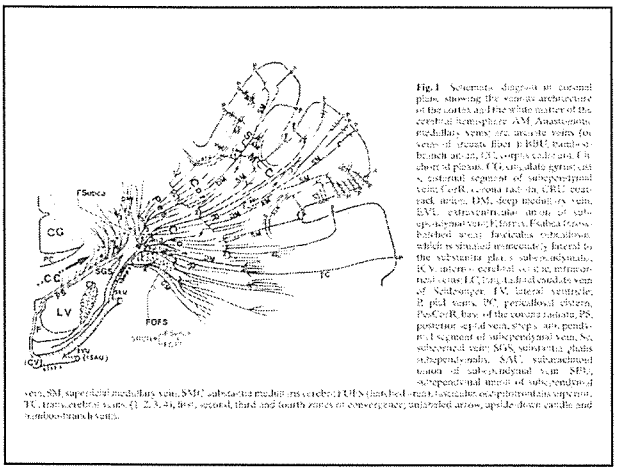
Trendelenburg G et al. Arch Neurol 2006

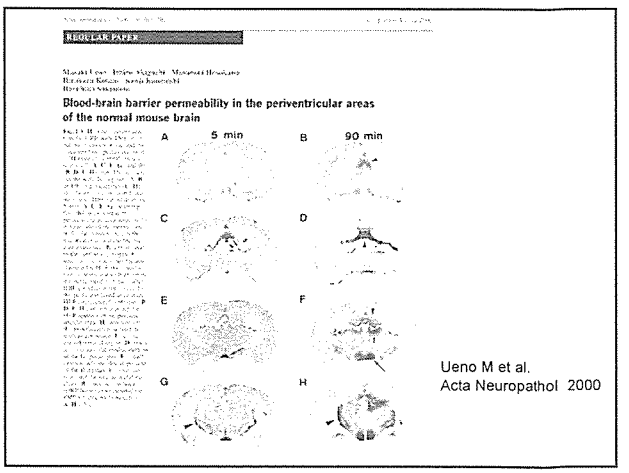
Roentgenogram of a 10mm thick injected coronal slice



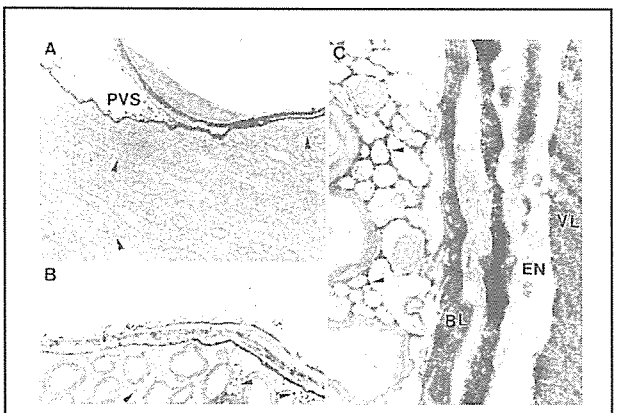
a: pial and parenchymal (including the lenticulostriate) arteries
b: arterial branching zones of medullary arteies

Okudera T et al. Neuropathology 1999

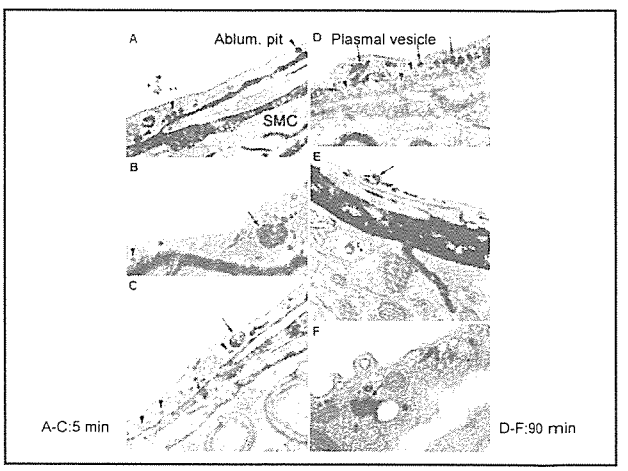




Ueno M et al.
Acta Neuropathol 2000



Electron micrographs of the vessels and their surroundings in the C3H mice perfusion-fixed after HRP circulation for 5 min (A,B) and 90 min (C)



Conclusion

1) It is necessary to consider the possibility of iNPH when we diagnose gait disturbance and parkinsonism in the elderly. In this consideration the most important indicators are the peculiar CT / MR images and the effect of CSF tap test.
2) Besides the symptomatic triad, we have to keep in mind the fourth sign : parkinsonian syndrome, which is often accompanied by reversible periventricular lucency in CT / MRI. In MRS study, reversible neuroaxonal hypoactivity is also shown in basal ganglia of iNPH.
3) Biopsy reports of brain specimens revealed 20 to 30% with AD pathology (definite AD:6%) and over 15% with brain ischemic change, however, the cause of iNPH has not been determined yet.

水頭症モデルにおける神経栄養因子
Neurotrophic Factors
in the
Hydrocephalic Model

Masaki Shinoda,
Mitsunori Matsumae,
Mituru Hidaka,
Lars Olson

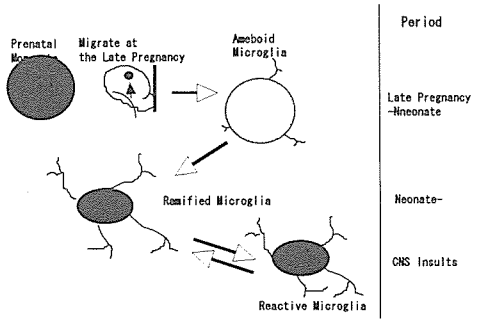
Today's Contents

Immunological Reaction in the Hydrocephalic Models
NGF family and Their Receptors in the Hydrocephalic Models
NT-3 Intraventricular Administration in the Hydrocephalic Models
GDNF (glial cell-line derived neurotrophic factors) in the Hydrocephlic Models

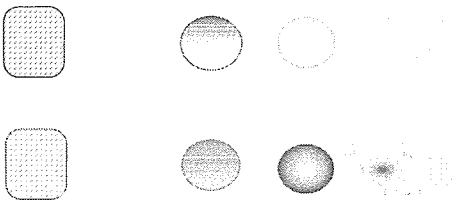
Today's Contents

Immunological Reaction in the Hydrocephalic Models
NGF family and Their Receptors in the Hydrocephalic Models
NT-3 Intraventricular Administration in the Hydrocephalic Models
GDNF (glial cell-line derived neurotrophic factors) in the Hydrocephlic Models

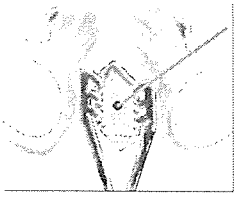
A Life of Microglia



MHC Loci and Microglial Status



Making A Hydrocephalic Model



Kaolin-induced hydrocephalus model

- Female Sprague Dawley rats (180-200 g) 0.1 ml of Kaolin (NacalaiTesque®, 250 mg/ml, suspended) injected into cisterna magna under halothane induced general anesthesia.
- Shams were injected with saline.

Materials and Methods

Kaolin-induced hydrocephalus model

- The hydrocephalic rats were sacrificed after 1 or 4 weeks, with pentobarbital anesthesia, killed by bleeding out, perfused and tissues were rapidly dissected and frozen.

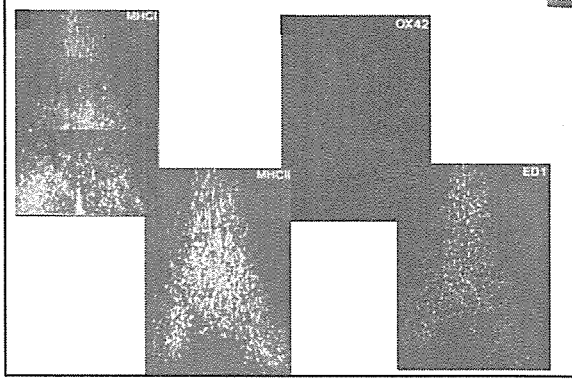
List of Antibodies

Antigen	Species	Dilution	Secondary Antibody	
GFAP	rabbit	1:100	anti-rabbit FITC (1:50)	Boheringer
TH	rabbit	1:300	anti-rabbit FITC (1:50)	Boheringer
NF	rabbit	1:400	anti-rabbit FITC (1:50)	Boheringer
OX-38	mouse	1:1000	anti-mouse FITC(1:50)	Amersham
OX-18	mouse	1:1000	anti-mouse FITC(1:50)	Amersham
OX-8	mouse	1:300	anti-mouse FITC(1:50)	Amersham
OX-42	mouse	1:200	anti-mouse FITC(1:50)	Amersham
OX-6	mouse	1:1000	-	
ED-1	mouse	1:300	anti-mouse FITC (1:50)	Amersham

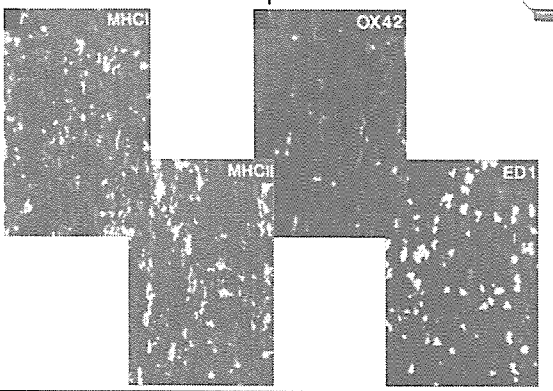
Reference

Shinoda M, Hudson JL, Stromberg I. et al. Brain Res, 680 (1995) 180-195.
Shinoda M, Hudson JL, Stromberg I. et al. Exp Neurol, 141 (1996) 173-180.
Shinoda M & Olson L. Int J Neurosci, 92 (1997) 9-28.

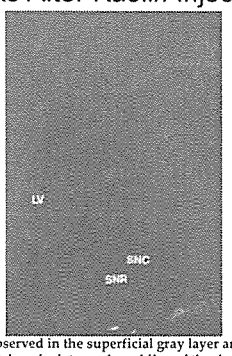
The Medial Septal Nucleus 8 Weeks After Kaolin Injection



Close-Ups of Cells in the Medial Septal Nucleus

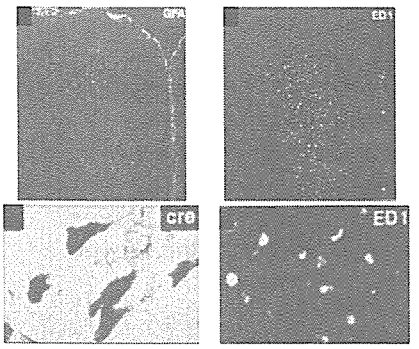


ED1 IR in the Midbrain 8 Weeks After Kaolin Injection



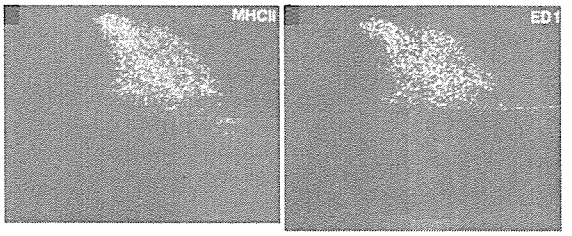
ED1-IR (+) cells were observed in the superficial gray layer and optic nerve layer of the superior colliculus, medial geniculate nucleus, hilus of the dentate gyrus and the interpeduncular nucleus. LV: lateral ventricle, SNC: pars compacta, SNR: pars reticulata.

Alteration of retrosplenic cortex



ED1-IR (+) microglia can be seen in layers II to V, only in retrosplenic cortex. Examples of dark and shrunken neurons (c) and reactive microglial proliferation in the same area (d).

Lower Pontine region
8 Weeks After Kaolin Injection



MHC class II-IR (+) and ED1-IR (+) microglial components in the medial and to a lesser extent the superior vestibular nucleus.

Results of Immunological Markers

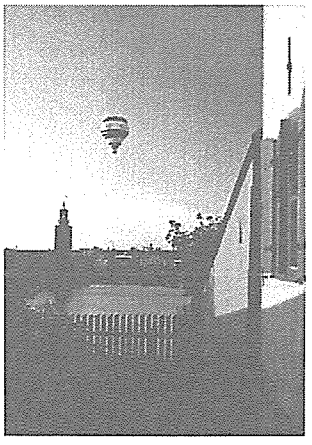
	Medial septal nucleus	Corpus callosum	Superior colliculus	Cerebellar peduncle	Ventral tegmental area	Retro splenic cortex	CDB+ cells entry into the brain	MHCII-cortical microglia
control	-	-	-	-	-	-	-	±
week1	±	+	-	-	±	±	±	+
week4	+	++	+	+	+	+	++	++
week8	++	++	++	++	++	++	±	+

Immunological Reactions in the Hydrocephalic Models

There are some target structures of immune reactions, like cholinergic systems, subcommissural organs, circumventricular organs and pontine cerebellar peduncles.

Even in control brain, choroidal and ependymal tissues are some immune marker positive, and following enlargement of the ventricles, ependymal structure became thinner, and a single layer arrangement, and choroidal tissue became shrunk and both of them increased expression of MHC class I.

ED1 positive microglial cells could be identified only in the retrosplenic cortex, and there were also "dark neurons" in light microscopic stainings. However, there were not so much ordinary GFA positive glioses.



Today's Contents

Immunological Reaction in the Hydrocephalic Models

NGF family and Their Receptors in the Hydrocephalic Models

NT-3 Intraventricular Administration in the Hydrocephalic Models

GDNF (glial cell-line derived neurotrophic factors) in the Hydrocephlic Models

Materials and Methods

Kaolin-induced hydrocephalus model

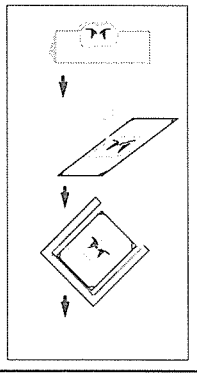
- Female Sprague Dawley rats (180-200 g) 0.1 ml of Kaolin (NacalaiTesque®, 250 mg/ml, suspended) injected into cisterna magna under halothane induced general anesthesia.
- Shams were injected with saline.
- The hydrocephalic rats were sacrificed after 1 or 4 weeks, with pentobarbital anesthesia, killed by bleeding out, and tissues were rapidly dissected and frozen.

Materials and Methods

In situ hybridization

- For in situ hybridization oligonucleotides probes (approximately 50 bp long) complementary to parts of mRNA encoding NGF, BDNF, NT-3, trkA, trkB and trkC were synthesized and radiolabelled with [a-35S] dATP at the 3' end using terminal deoxyribonucleotidyl transferase to a specific activity of 1-3 x 10^7 cpm/mg.

In situ Hybridization for This Study



Cut Sections: 14 μm fo each sctions.

Probe Preparation:

Oligonucleotide probes (approximately 50 bp long) complementary to parts of mRNA encoding NGF, BDNF, NT-3, trkA, trkB and trkC were synthesized and radiolabelled with [35S] dATP at the 3' end using terminal deoxynucleotidyl transferase.

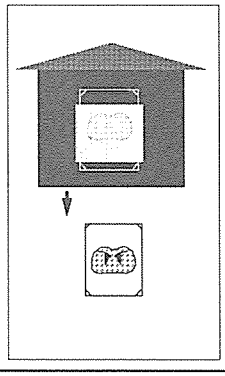
Hybridization:

for 16-18 hours at 42°C in a humidified chamber at least 0.5 ng probe/ slide (150,000 cpm/μl) ina mixture of 4 x SSC, 50 % formamide, 1 x Denhardt's solution, 1% sarcosyl, 0.02 M phosphate buffer (pH 7.0),10% dextran sulfate, 500 μg/ml heat denatured salmon sperm DNA and 200 mM dithiothreitol.

Rinse :

5 x 15 min at 55°C in 1 x SSC, to room temperature, dipped in distilled water and dehydrated through graded ethanol (75 %, 95 %, 99.5 %) and air dried.

In situ Hybridization for This Study



Autoradiography:

Slides were dipped in emulsion, dried,placed in boxes and exposed for 8 weeks at 4°C. The emulsion on the sections was then developed and fixed.

Rinse and Light Microscopic Staining:

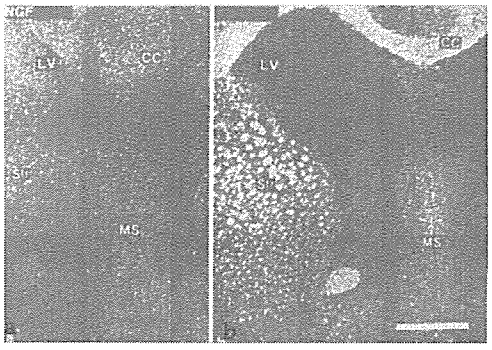
Rinse in water and then the slides were lightly counter stained with cresyl-violet or toluidin-blue and mounted.

Materials and Methods

NT-3 Enzyme Immunoassay

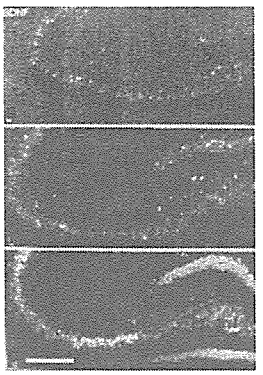
- Another rats were injected with kaolin and killed after 4 weeks. The monoclonal antibody 3W3 was coated onto EIA microplates (0.5 μg/ml). The samples were added in a volume of 50 μl.
- Parallel control wells received an excess of 3W3 antibody together with sample (5 μl of the antibody solution to give a final concentration of 0.5 μg/ml).
- To determine immobilized NT-3, the 3W3 antibody conjugated to β-galactosidase was added using 3-maleimido-benzoyl-N-hydroxy-succinimide ester (MBS, Sigma).

NGF mRNA in the severe hydrocephalus



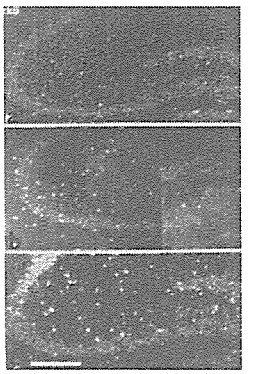
corpus callosum (CC), striatum (Str), medial septal nucleus (MS). (a) control. (b) severe ventricular enlargement, week 4.

BDNF mRNA of hippocampus



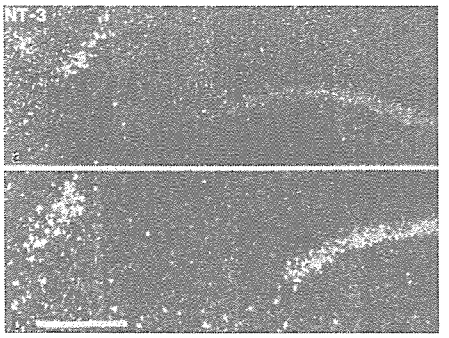
(a) control. (b) medium ventricular enlargement, week 1. (c) large, week 4.

trkB mRNA of hippocampus



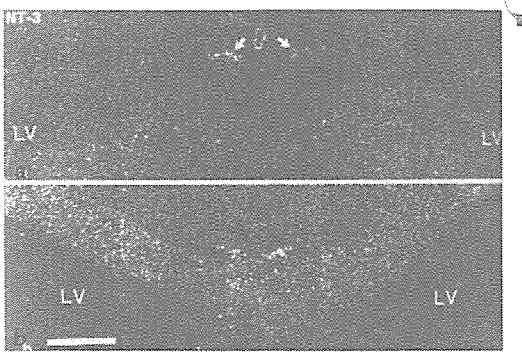
(a) control. (b) medium enlargement, week 1. (c) medium enlargement, week 4.

NT-3 mRNA of hippocampal CA2 and the dentate gyrus



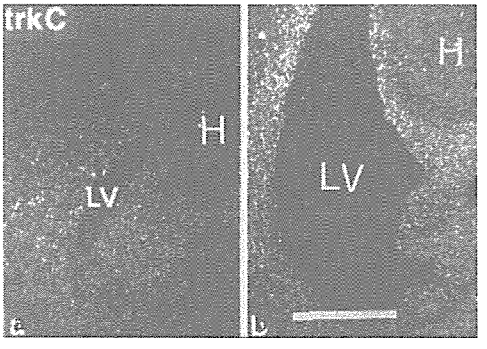
(a) control. (b) medium ventricular enlargement, week 1.

NT-3 mRNA of corpus callosum



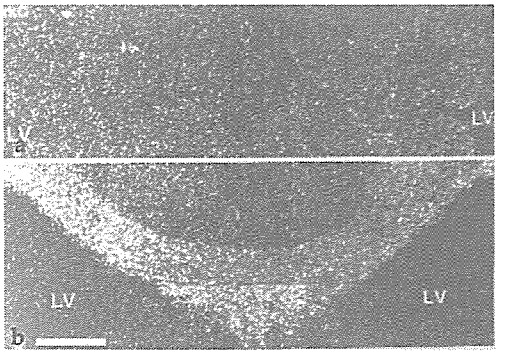
(a) control,. (b) large ventricular enlargement, week 4. LV; lateral ventricle.

trkC mRNA of peri ventricular region



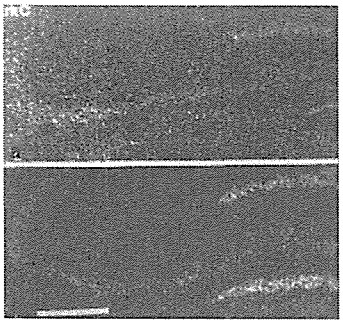
(a) control. (b) large ventricular enlargement, week 4. H; hippocampus, LV; lateral ventricle.

trkC mRNA of corpus callosum



(a) control. (b) large ventricular enlargement, week 4. LV; lateral ventricle.

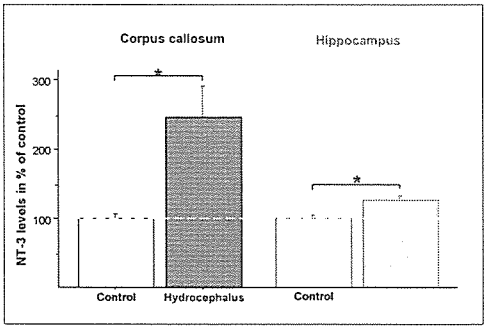
trkC mRNA of hippocampus



(a) control. (b) medium ventricular enlargement, week 1.

The moderate ventricular enlargement group showed the highest trkC mRNA expression. Following further enlargement of the ventricle, trkC mRNA expression was decreased.

EIA measurement of NT-3 in corpus callosum and hippocampus



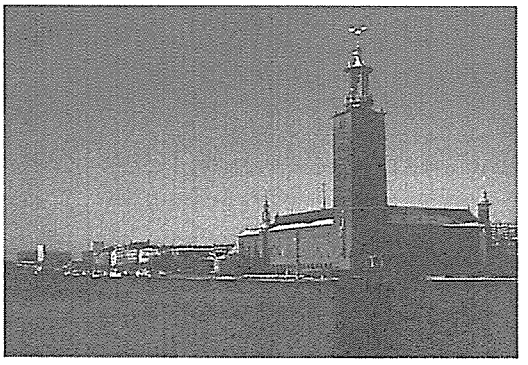
The hydrocephalic corpus callosum showed 151 %, and hippocampus 26 % increase from control levels ($p < 0.05$, Students T-test).

Results from the *in situ hybridization* studies

area	ventricle	NGF	BDNF	NT-3	trkA	trkB	trkC
CA1							
	large						
CA2							
	large						
CA3							
	large						
CA4							
	large						
Dentate Gyrus							
	large						
Corpus callosum							
	large						
Striatum							
	large		NS	NS		NS	NS
Medial septal nucleus							
	large		NS	NS		NS	NS

Neurotrophins and trks in the Hydrocephalic Models

- 1) The Medial Septal and Striatal NGF mRNA Levels Increased with Severity of Hydrocephalus.
- 2) The Hippocampal trkB and BDNF mRNA Levels Increased with Time in Animals with Ventricular Enlargement.
- 3) From the Point of View of Severity of the Hydrocephalic Condition, Expression of Hippocampal trkB, trkC and NT-3 mRNA Increased in Animals with Moderate Ventricular Enlargement, while it Decreased in the Large (Severe) Ventricular Enlargement Group.
- 4) In corpus callosum There was an Apparent NGF, NT-3 and trkC mRNA, but not trkA, Increase in Hydrocephalic Animals.
- 5) NT-3 EIA Confirmed the Presence of NT-3 Protein Increases in corpus callosum.



Today's Contents

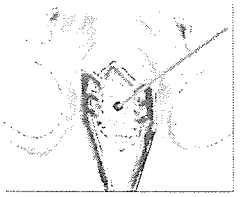
Immunological Reaction in the Hydrocephalic Models

NGF family and Their Receptors in the Hydrocephalic Models

NT-3 Intraventricular Administration in the Hydrocephalic Models

GDNF (glial cell-line derived neurotrophic factors) in the Hydrocephlic Models

Making A Hydrocephalus



Kaolin-induced hydrocephalus model

- Female Fisher 344 rats (180-200 g) 0.1 ml of Kaolin (NacalaiTesque®, 250 mg/ml, suspended) injected into cisterna magna under halothane induced general anesthesia.

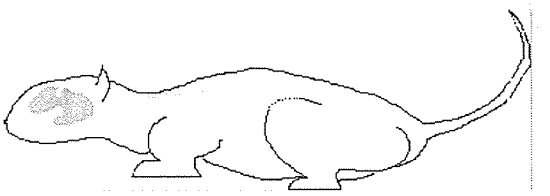
NT-3 Intraventricular Administration

Alzet® Osmotic Pump 2002 was implanted 1 Week After kaolin injection.

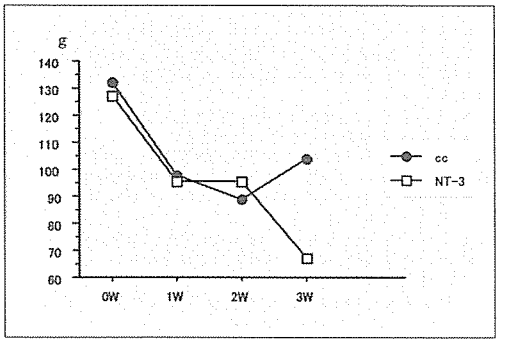
10 mg of Human Recombinant NT-3 (Austral Bio®) had administrated with brain infusion kit.

Shams were used with same amount of cytochrome-c.

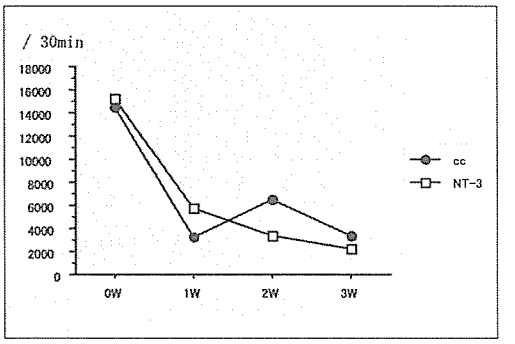
3 Weeks after the implantation, all rats were Sacrificed.



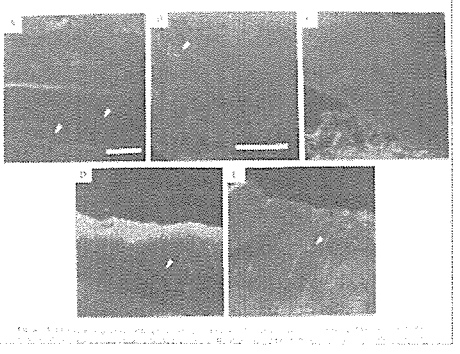
Alterations of Body Weights After NT-3 administration



Alterations of Rotational Behaviors After NT-3 administration



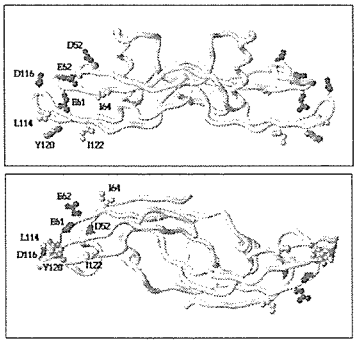
Immunological Markers After NT-3 Administration



Intraventricular NT-3 Administration

- The MHC class I-IR positive microglial proliferations were revealed in the olfactory nerve and the anterior commissure.
- Lesser amounts of glial elements were detected in the NT-3 treated groups.
- There were no curative effects in the NT-3 treated group.

Glial cell line-derived neurotrophic factor (GDNF) in the Hydrocephalic Model



Today's Contents

Immunological Reaction in the Hydrocephalic Models

NGF family and Their Receptors in the Hydrocephalic Models

NT-3 Intraventricular Administration in the Hydrocephalic Models

GDNF (glial cell-line derived neurotrophic factors) in the Hydrocephlic Models

GDNF

(glial cell line-derived neurotrophic factor)

GDNF was initially purified and cloned from a glial cell line in the search for a neurotrophic factor for midbrain DA neurons that degenerate in Parkinson Disease.

Recent studies have extended the spectrum of GDNF bioactivities to a variety of central and peripheral neurons as well as to the kidney and gut.

GDNF mRNA Distribution

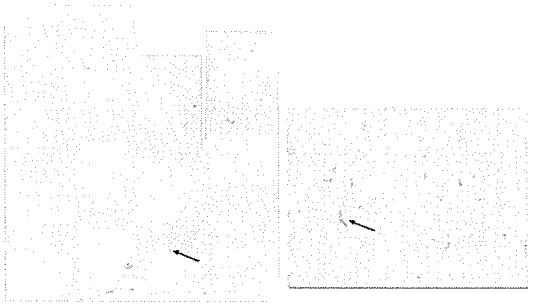
In the nigrostriatal system, including embryonic and neonatal striatum, embryonic ventral midbrain and substantia nigra Type I astrocytes.

While GDNF mRNA was undetectable in normal adult rat central nervous system (CNS) by in situ hybridization, it was upregulated in seizure-induced striatum, hippocampus and neocortex, suggesting a possible role for GDNF in response to injury.

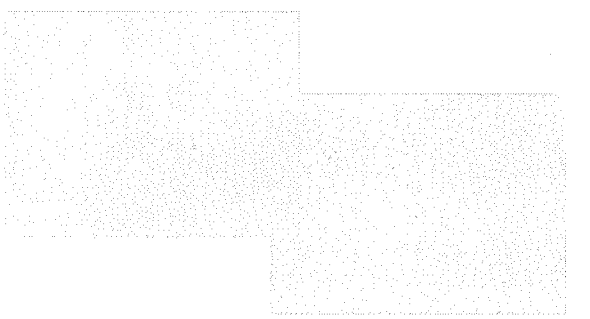
Roles of GDNF

In the CNS, GDNF has potent trophic effects on midbrain DA neurons, facial and spinal motoneurons, LC noradrenergic neurons and cerebellar Purkinje cells. GDNF also has protective effects on hippocampal, thalamic and amygdaloid neurons. In the periphery, GDNF acts on sympathetic and parasympathetic autonomic as well as various subpopulations of sensory neurons.

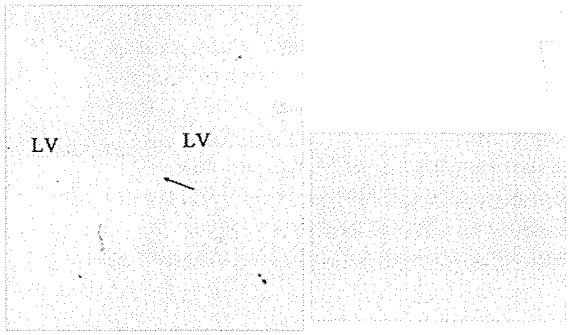
GDNF mRNA upregulated in Early Treatment Moderate Hydrocephalus



No GDNF mRNA in Severe Hydrocephalus



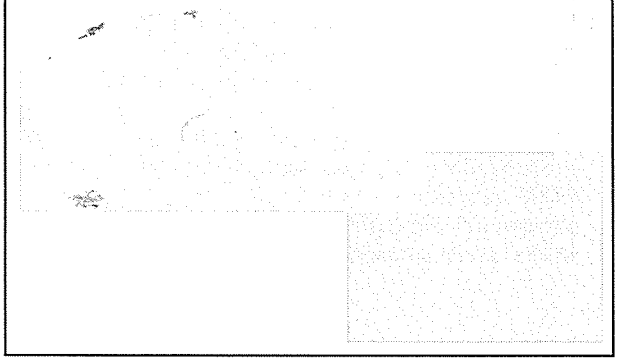
GDNF mRNA is upregulated in the Lateral Septal Nucleus



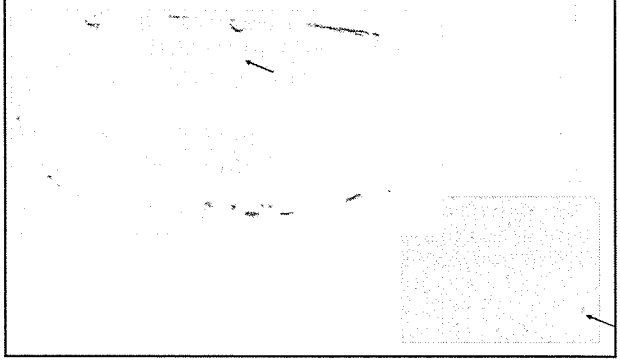
Results & Conclusions

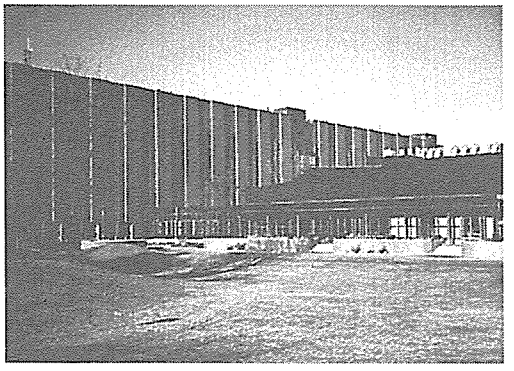
- Nigral GDNF mRNAs were upregulated in early treatment and moderate hydrocephalus (but not significant).
- In severe hydrocephalus, GDNF were upregulated in the lateral septal nucleus.
- GDNF mRNA distributions were not well correlated with Neurotrophins and trks mRNAs distributions in the kaolin-induced hydrocephalus.

GDNF mRNA in The Early and Moderate Hydrocephalic Spine

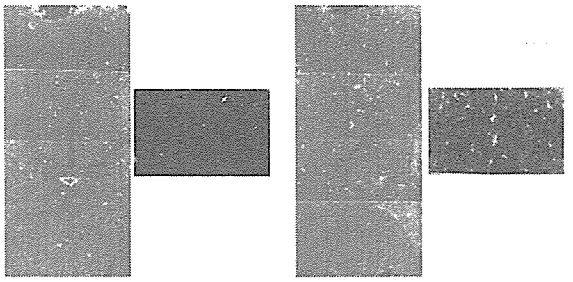


GDNF mRNA in The Severe Hydrocephalic Spine



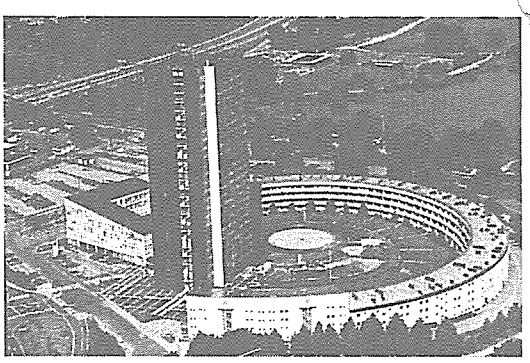


Activated Microglial Proliferaion and NGF IR Upregulation in The Hydrocephalic Spine



Reactive Microglia ED1-IR

NGF (nerve growth factor)IR



Acknowledgements

- The authors thank Susanne Almström, Servet Eken, Monica Casserlöw and Karin Lundströmer for expert technical assistance, and Ida Engqvist for editorial support.
- We also thank Drs. Rolf Zetterström, Jobu Itoh, Satoshi Kobayashi for their valuable comments.
- This study was supported by the Swedish MRC, US public health grants and Japanese basic research grant (general-c) 09671452.

NPHの精神症状の特徴

国立精神・神経センター国府台病院
精神科　早川達郎

2006.8.27　正常圧水頭症と関連疾患の病因・病態と治療に関する研究班　平成18年度夏季ワークショップ

過去の報告では

NPHの精神症状は、精神運動抑制、発動性低下など、うつ病に類似した症状を呈する、と報告しているものが多くみられる。(活動性低下症状)

その一方で、焦燥、情緒的な不安定さ、攻撃性等の活動性亢進症状を呈した症例も報告されている。

CASE REPORT

68歳男性

主症状：4週間続いている妄想とそれに基づいた攻撃的行動、18ヶ月続いている軽度認知機能障害、および3ヶ月続いている顕著な人格変化(攻撃性と非協調性)

彼は近隣の人たちと家族が共謀して、彼の預金通帳を盗もうとしていると思い込み、近隣の女性を絞殺しようと試み、自宅をガス爆発させると脅し、またナイフやエアピストルを持っていた。NPHの診断のもとシャント手術施行され、精神症状は改善。

Pinner G et al. : Psychiatric Manifestations of Normal-Pressure Hydrocephalus: A Short Review and Unusual Case. International Psychogeriatrics 9:465-470,1997

精神疾患の診断分類では、NPHの精神症状は、器質性精神障害に分類される

器質性精神障害では、その疾患とは無関係に一定のパターンで出現する精神症状と、疾患にある程度特徴的な精神症状が種々の程度に混在して出現するという特徴がある。

NPHで出現しうる精神症状

・器質性精神障害に共通した精神症状

・NPHに特徴的な精神症状？
　局在症候としての精神症状
　前頭葉症候群、側頭葉症候群など

これらの精神症状が種々の程度に混在して出現してくるものと考えられる。

器質性精神障害に共通した主な精神症状

1)意識障害
2)認知症、人格変化 → 急性期：意識障害に基づいた精神症状(せん妄など)
3)健忘症候群
4)幻覚、妄想
5)感情障害、意欲障害 → 慢性期：不可逆な認知症と人格変化

NPHに特徴的な精神症状

活動性低下症状：発動性の低下

活動性亢進症状：焦燥、情緒的な不安定さ、攻撃性

活動性亢進症状に着目し、前頭葉機能障害との関連性を検討する

前頭葉機能障害に基づく精神症状

臨床症状として、発動性の低下、常同行為、保続、思考障害、社会的な行動障害、情動の障害などさまざまな症状が出現すると言われている。

→ 発動性の低下
行為・行動異常
情動の障害

発動性の低下

最近になり、前頭葉の中でも特に前頭前野の機能低下がうつ病の病態発生機構の一部を説明するとして注目されている。

うつ病患者の前頭前野における血流量の低下や糖代謝の低下が報告されている。

行為・行動異常

ルーチン化された行動、場合によっては生来的な行動様式を抑制することができなくなり、容易に出現するようになる

・相手の動作を真似する
・運動保続、言語反復
・目の前の物品を使い出す
・常同行動
・無意味なものをむやみに集める

情動の障害

前頭前野眼窩部は大脳辺縁系との機能的関係が強いことから、この部位が損傷された場合には、さまざまな情動の障害が起こりうるものと考えられる。

前頭葉機能障害に基づいた行為・行動異常および情動の障害は、NPHにおける活動性亢進症状（焦燥、情緒的な不安定さ、攻撃性等）の基盤となりうる

発動性の低下 ・・・・・ 活動性低下症状

行為・行動異常
情動の障害
} 活動性亢進症状

NPHの活動性亢進症状を評価するにあたってなんらかの尺度が必要

Cohen-Mansfield Agitation Inventory（CMAI）は焦燥を定義したり評価するための特異的な尺度の一つである。

CMAI　介護者により点数付けされる

1=認められない，2=週に一度以下，3=週に一度もしくは2度くらい，4=週に3回以上，5=一日に1,2回，6=1日に3回以上，7=1時間に2回以上

1.全般的に何でも繰り返すことが多い	13.性的なことをする（行動）	25.叩く
2.関係のあることで話に割り込む	14.座っていても落ち着かずモジモジしている	26.蹴る
3.関係のない事柄で話に割り込む	15.部屋の中を行ったり来たりする	27.物を投げる
4.奇妙な音を出す	16.別の場所に行こうとする。	28.破壊行動（物を壊す、引き裂く）
5.大声で叫ぶ	17.不適切な衣服の着脱	29.人にくっつく、すがりつく
6.不平や泣き言を言う。	18.反復衒奇（わざとらしいことを繰り返す）	30.押す
7.ひっきりなしに注意を促す	19.物を不適切に扱う	31.噛みつく
8.拒絶症	20.物をひっつかむ、ひったくる	32.引っ掻く
9.ののしる	21.物を隠す	33.自傷行為
10.唾を吐き散らす	22.自分が隠れる	34.他害行為
11.威張った言葉遣いをする	23.奇妙な動きStrange movement	35.わざと転ぶ、倒れる
12.性的なことを言う	24.かんしゃくを起こす	36.食べ物以外の物を口にする

CMAI

1.全般的に何でも繰り返すことが多い
2.関係のあることで話に割り込む
3.関係のない事柄で話に割り込む
4.奇妙な音を出す
5.大声で叫ぶ
6.不平や泣き言を言う。
7.ひっきりなしに注意を促す
8.拒絶症
9.ののしる
10.唾を吐き散らす
11.威張った言葉遣いをする
12.性的なことを言う
13.性的なことをする（行動）
14.座っていても落ち着かずモジモジしている
15.部屋の中を行ったり来たりする
16.別の場所に行こうとする。
17.不適切な衣服の着脱
18.反復衒奇（わざとらしいことを繰り返す）

CMAI

19.物を不適切に扱う
20.物をひっつかむ、ひったくる
21.物を隠す
22.自分が隠れる
23.奇妙な動きStrange movement
24.かんしゃくを起こす
25.叩く
26.蹴る
27.物を投げる
28.破壊行動（物を壊す、引き裂く）
29.人にくっつく、すがりつく
30.押す
31.噛みつく
32.引っ掻く
33.自傷行為
34.他害行為
35.わざと転ぶ、倒れる
36.食べ物以外の物を口にする

CMAI項目中の前頭葉機能障害に基づくと考えられる行為・行動異常

1.全般的に何でも繰り返すことが多い
3.関係のない事柄で話に割り込む
7.ひっきりなしに注意を促す
15.部屋の中を行ったり来たりする
16.別の場所に行こうとする。
18.反復衒奇（わざとらしいことを繰り返す）

→CMAIは前頭葉機能障害に基づく焦燥の評価に有用

今後の課題

精神症状を呈するNPHの中でも、発動性の低下など活動性低下症状を認める群と、焦燥など活動性亢進症状を認める群がある。両群間の違いについて、画像所見も含め検討していく必要がある。

また、症例を積み重ねることにより、NPHに特徴的な精神症状を、より詳細に検討し、精神科医がNPHを見逃さないように啓蒙していく必要があると考える。そのための手段の一つとして、CMAIによる評価は有用であると考える。