2014 年中區失智症夏季季會

Vascular risk factors and dementia

時間: 103 年 6 月 28 日(六)

地點: 台中永豐棧酒店（407 台中市西屯區臺灣大道二段 689 號）

主辦單位: 光田醫院、新菩提醫院

協辦單位: 臨床失智症學會、神經學學會、老人精神醫學會、老人醫學會、精神醫學會

Opening and introduction	光田醫院 孫明輝醫師	15:30-15:50

座長　彰化基督教醫院 王文甫醫師

1. Hypertension and dementia 光田醫院 孫明輝醫師	15:50-16:30
2. Diabetes and dementia 林新醫院 劉彥良醫師	16:30-17:10
3. Hyperlipidemia and dementia 新菩提醫院 邱百誼醫師	17:10-17:50
Closing and panel discussion 新菩提醫院 邱百誼醫師	17:50-18:10

Curriculum Vitae

基本資料

姓名： 孫明輝　　Ming_Hui, Sun

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主要學歷

畢業學校	國別	主修系所	學位	起迄年月(西元年/月
國立台灣大學	本國	醫學系	學士	1982/09 至 1989/06
中山醫學大學	本國	醫學研究所	碩士	2001/09 至 2003/06

License and Certificate

醫師證書： 醫字 第 018583 號
神經科專科證書： 神專醫字 第 000313 號
教育部部定講師：講字 第 089607 號

現職及與專長相關之經歷：

服務機關	服務部門	職稱	起迄年月
現職			
弘光科技大學	護理系	兼任講師	2007/02 ~
光田綜合醫院	神經內科	主治醫師	1994/11 ~
光田綜合醫院	神經內科	主任	2007/12~
經歷			
台中市立老人醫療保健醫院		主治醫師	1994/11 至 2001~09
台灣大學附設醫院	神經部	住院醫師	1991/07 至 1994/11

Memberships of Academic Societies

台灣神經學學會
台灣腦中風學會
中華民國醫用超音波學會
台灣醫學會
台灣癲癇醫學會
台灣臨床失智症學會
American Stroke Society

Publications：

1. JH Yeh, MH Sun, HC Chiu, Dominant-Inherited Hypokalemic periodic paralysis in a large Chinese family, J Formos Med Assoc 1999; 98:277-82
2. CS Liu, MH Sun, CL Kuo, CS Tsai, HC Lu, ML Hsieh Molecular, clinical studies in spinocerebellar ataxia type2, The Changhua Journal of Medicine 2001;6:107-112
3. YS Tsai, MH Sun, CM Chen, HW Kuo, LC Hung. Factors associated with hospital delays after acute ischemic stroke. Mid-Taiwan Journal of Medicine 2003; 8:s1 36-42
4. 蔡宜秀, 孫明輝, 洪麗珍, 郭憲文, 影響某區域醫院缺血性腦中風初患病患住院醫療費用之相關因素. 中台灣醫誌 2008; 13: 143-51

5. 楊清鎮, 孫明輝, 破傷風-可預防的致病疾病. 感染控制雜誌 中華民國 98 年 4 月第十九卷第二期
6. Nai-Yuan Lee, Ming-Hui Sun, and Wang-Sheng Ko. Effect of hyperglycemia on the changes of intracellular [ca2+]i in heart myoblast *The Chinese Journal of Physiology*. 2010;536.
7. Fang-I Hsieh L-ML, Sien-Tsong Chen, Chyi-Huey Bai, Mu-Chien Sun, Hung-Pin Tseng, Yu-Wei Chen, Chih-Hung Chen, Jiann-Shing Jeng, Song-Yen Tsai, Huey-Juan Lin, Chung-Hsiang Liu, Yuk-Keung Lo, Han-Jung Chen, Hou-Chang Chiu, Ming-Liang Lai, Ruey-Tay Lin, Ming-Hui Sun, Bak-Sau Yip, Hung-Yi Chiou, and Chung Y. Hsu. Aha/asa get with the guidelines – stroke performance indicators: Surveillance of stroke care in the taiwan stroke registry. *Circulation*. 2010; 122:1116-1123. **(SCI)**

學會論文

1. MH Sun , RM Wu, HC Chiu, M Wang Risk factors on the occurrence of response fluctuations and dyskinesias in the parkinson's disease 中華民國神經學學會會刊 1992
2. MH Sun, YC Chang 正常人之心率變異性: 以 RR 間距之變異係數及心率差距表示 Heart rate variability in healthy subjects – expressed as coefficient of variance of RR intervals and range of heart rate. 中華民國神經學學會會刊 1994
3. CH Yeh, MH Sun, CS Liu, WS Ko, LY Ko Granulocytic sarcoma presenting as an epidural cord compression 中華民國神經學學會會刊 1996
4. MH Sun, CS Liu, HM Wu, SJ You, YH Wei, M Hsieh Molecular and clinical studies of SCA2 中華民國神經學學會會刊 1998
5. MH Sun, CS Liu, HM Wu, SJ You, LY Ko Late-life migraine accompaniments presented as march of myoclonus 台灣神經學學會會刊 1999
6. CS Liu, MH Sun, HW Chen, CK Lii, YH Wei Increase of RBC fragility and disturbance of glutathione homeostasis in Machado-Joseph Disease 台灣神經學學會會刊 2000
7. MH Sun Posterior reversible encephalopathy syndrome presented as pontine edema is not necessarily a benign condition: 2 case report 台灣神經學學會會刊 2006
8. MH Sun, YH Tsai, LY Ko Subtypes of acute ischemic stroke in mid-Taiwan: Stroke registry in a regional hospital 台灣腦中風學會大會會刊 2006

9. YH Tsai, MH Sun, LY Ko Outcome and disposition after hospitalization for acute ischemic stroke n MidTaiwan: Stroke registry in a regional hospital 台灣腦中風學會大會會刊 2006
10. MH Sun, HU Tsai Hypoalbuminemia is an independent predictor for poor outcome in acute ischemic stroke 台灣腦中風學會大會會刊 2006

Study Experience:

1. A prospective post-marketing surveillance (PMS) study describing the safety/tolerability and efficacy of Exelon® in patients with Alzheimer's disease.
2. 台灣地區多醫院腦中風登錄計畫 (Taiwan stroke Registry)
3. 建立以中風病人爲中心之社區整合性照護模式 (A pilot study for developing a stroke care mode)
4. ASP I (Ancrod stroke program) Study of Acute Viprinex™ for Emergency Stroke: A randomized, double-blind, placebo-controlled study of Ancrod in subjects beginning treatment within 6 hours of the onset of acute ischemic stroke.
5. A phase II, double-blind, placebo-controlled, dose-finding study in patients with diabetic neuropathic pain to evaluate efficacy and safety of TAK-583
6. A Randomized, Double-blind, Placebo-and Active-Controlled Study of Carisbamate in the Treatment of Neuropathic Pain in Diabetic Peripheral Neuropathy followed by a Blinded Extension Phase (CARISNPP2003)
7. The Safety and Efficacy of Cilostazol in Ischemic **S**troke Patients with Peripheral Arterial Disease (SPAD Study)
8. PG2 Injection 500mg in acute stroke study (PASS)
9. A double-blind, randomized, placebo-controlled, multicenter study to compare functional outcome and safty of treatment with BNG-1 in combination with aspirin with that of aspirin alone in ischemic stroke recovery (BNG-TW002)

Hypertension and dementia

孫明輝

光田綜合醫院 神經內科

Hypertension, a major risk factor for stroke, is also a leading cause for vascular cognitive impairment (VCI). Alzheimer's disease (AD) and VCI are the most common forms of dementia. Up to 50% cases of dementia have mixed pathology featuring both vascular (VCI) and neurodegenerative lesions (AD). There are increasing evidence indicates that hypertension is also a risk factor for AD. Midlife hypertension doubles the risk for AD later in life and accelerates the progression of the dementia.

In this speech, I will discuss the following topics: 1) how hypertension alters the cerebrovascular structure and function, 2) the brain lesions underlying VCI and 3) the interaction between hypertension and AD. I will also briefly review the randomized clinical trials and observational clinical studies for antihypertensive therapy and prevention of prevention.

劉彥良醫師
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經歷：
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衛生福利部彰化醫院神經科主治醫師/主任
林新醫院神經科主治醫師

Diabetes mellitus and dementia

Abstract:

Higher glucose levels may contribute to an increased risk of dementia through several potential mechanisms, including acute and chronic hyperglycemia and insulin resistance and increased microvascular disease of central nervous system.

There is an urgent need for new ways to treat Alzheimer's disease (AD), the most common cause of dementia in the elderly. Current therapies are modestly effective at treating the symptoms, and do not significantly alter the course of the disease. Over the years, a range of epidemiological and experimental studies have demonstrated interactions between diabetes mellitus and AD. As both diseases are leading causes of morbidity and mortality in the elderly and are frequent co-morbid conditions, it has raised the possibility that treating diabetes might be effective in slowing AD. This is currently being attempted with drugs such as the insulin sensitizer rosiglitazone. These two diseases share many clinical and biochemical features, such as elevated oxidative stress, vascular dysfunction, amyloidogenesis and impaired glucose metabolism suggesting common pathogenic mechanisms

The most important common mechanism between insulin-resistant (type II) diabetes and AD could be impaired insulin signaling; a form of toxic amyloid can damage neuronal insulin receptors and affect insulin signaling and cell survival. It has even been suggested that AD could be considered as "type 3 diabetes" since insulin can be produced in brain. Another common feature of diabetes and AD are increased advanced glycation endproduct-modified proteins are found in diabetes and in the AD brain; the receptor for advanced glycation endproducts plays a prominent role in both diseases. Although clinical trials of certain types of diabetic medications for treatment of AD have been conducted, further understanding the common pathological processes of diabetes and AD are needed to determine whether these diseases share common therapeutic targets.

邱百誼

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經歷

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曾任台灣神經學會神經心理暨神經精神學組委員
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曾任中國醫藥大學台中附設醫院神經部主治醫師
曾任中國醫藥大學北港附設醫院神經內科主任

著作

1. **Chiu PY**, Chen PK, Tsai JT, et al. Freqeuncy of early and late-onset dementias in a Taiwanese dementia clinic: first report on the Lin-Shin Dementia Registry Project. (submitted)
2. **Chiu PY**, Chen PK, Lai TL, et al. Depression in Dementia with Lewy bodies: Compared with Alzheimer's disease. (submitted)
3. Chen PK, **Chiu PY**, Tsai IJ, et al. Onset headache predicts good outcome in patients with first-ever ischemic stroke. doi: 10.1161/STROKEAHA.113.67707.
4. **Chiu PY,** Steffens D, Chen PK, Hsu YC, Huang HT, and Lai TJ. Depression in Taiwanese patients with Alzheimer's disease: Determined with National Institute of Mental Health Provisional Criteria. International Psychogeriatr. 2012;14:1-7 (SCI).
5. Chen PK, Fuh JL, Lane HY, **Chiu PY**, Tien HC, Wang SJ. Morning headache in habitual snorers: Frequency, characteristics, predictors and impacts. Cephalalgia 2011;31: 829-36. (SCI)
6. **Chiu PY**, Dai DE, Hsu HP, Lee C, Lin JJ, Kuo HC, Huang YH, Liu, YC, Tasi, CP. Safety, tolerability and efficacy of rivastigmine in Taiwanese patients with

Alzheimer's disease: Results of a prospective post-marketing surveillance study. Drug Investig. 2009;29:729-38. (SCI)

7. **Chiu PY,** Liu CH, Tsai CH. Neuropsychiatric manifestations in vascular cognitive impairment patients with and without dementia. Acta Neurol Taiwan. 2007;16:86-91.
8. Yang YW, Tasi CH, Chang FC, Lu MC, *__Chiu PY__. Reversible paraneoplastic limbic encephalitis caused by a benign ovarian teratoma: report of a case and review of literatures. J Neurooncol 2006;80:309-12 (SCI) *Corresponding author.
9. **Chiu PY**, Chung CL. Delusions in patients with very mild, mild and moderate Alzheimer's disease. Acta Neurol Taiwan 2006;15:21-5.
10. Huang WS, **Chiu PY**, Kao A, et al. Detecting abnormal regional cerebral blood flow in patients with primary Sjogren's syndrome by technetium-99m ethyl cysteinate dimer single photon emission computed tomography of the brain--a preliminary report. Rheumatol Int 2003;23:174-7. (SCI)
11. Huang WS, **Chiu PY**, Kao A, et al. Decreased cerebral blood flow in Neuro-Behcet's sydrome patients with neruopsychiatric manifestations and normal magnetic resonance imaging- A preliminary report. J Neuroimaging 2002;12:355-9. (SCI)
12. Huang WS, **Chiu PY**, Tsai CH, et al. Objective evidence of regional erebral blood flow in patients with systemic lupus erythematosus on Tc-99m ECD brain SPECT. Rheumatol Int 2002;22:178-81. (SCI)
13. **Chiu PY**, Huang WS, Lee CC, et al. An unusual case of tuberculous meningitis. Mid Taiwan J Med 2001;6:119-23.
14. Liu CH, Lee CC, **Chiu PY**, et al. C-*jun* Expression in Patients with Parkinson's Disease. Mid Taiwan J Med 1999;4:104-8.

壁報論文

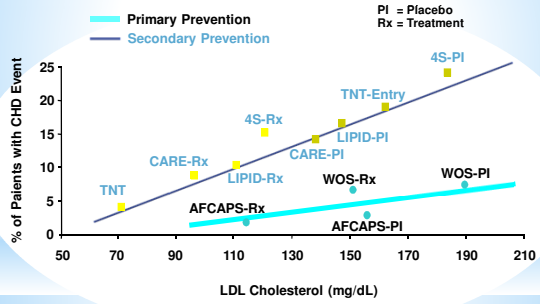
1. Chiu PY, Lai TJ. Psychosis in normal pressure hydrocephalus. 台灣老年精神醫學會 2014.
2. **Chiu PY**, Lai TJ. Rivastigmine patch in the one-year treatment of mild to moderate Alzheimer's disease and Parkinson's disease dementia. The 16th International Psychogeriatric Association International Congress. IPA 2013.
3. **Chiu PY**, Lai TJ. Performance on the Frontal Assessment Battery Test in Dementia with Lewy Bodies and Alzheimer's Disease. The 11th Alzheimer's and Parkinson's Disease Conference AD/PD 2013.
4. Lai TJ, **Chiu PY**, Lin JH. Hallucinations in Subcortical Vascular Dementia. 台灣老年精神醫學會 2013.

5. **Chiu PY**, Yang YW, Tsai CW. Neuropsychiatric profiles in patients with Dementia with Lewy bodies: Comparison with Alzheimer's disease and Parkinson's disease with dementia. 台灣神經學學會 2007.
6. **Chiu PY**. Early diagnosis of Dementia with Lewy Bodies. 台灣神經學學會 2006.
7. **Chiu PY**, Hsieh SL, Tasi CH. Attention shifting deficits in Parkinson's disease. 台灣神經學學會 2005.

Hyperlipidemia and dementia

邱百誼
新莊提醫院 神經內科

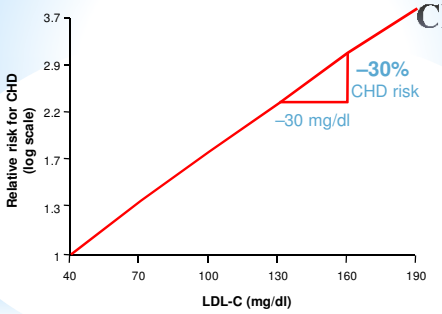
Relation Between CHD Events and LDL Cholesterol in Statin Trials



AFCAPS: Lovastatin; 4S: Simvastatin
WOS, LIPID, CARE: Pravastatin

Kastelein. Atherosclerosis 1999;143:S17-S21

Lower LDL-C Reduces Risk for CHD



Adapted from Grundy SM et al *Circulation* 2004;110:227–239.

The association between VRFs and an increased risk of developing dementia

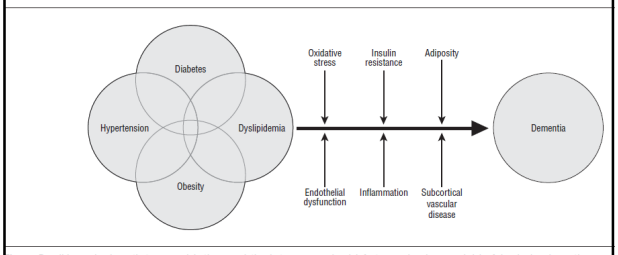


Figure. Possible mechanisms that may explain the association between vascular risk factors and an increased risk of developing dementia.

Laura E et al., Arch Neurol. 2009;66(10):1210-1215

Natural history of BP, cholesterol and AD

- ApoE E4, high midlife total cholesterol and midlife BP are independent AD risk factors[1]

BUT.....

- BP and cholesterol of AD patients not higher than controls
- Cholesterol levels gradually ↓with age[2]
- More rapid ↓in those who develop dementia[2]

[1]Kivipelto et al, *Neurology* 2001;56:1683-1689
[2]Kivipelto et al, *CNS Drugs* 2002; 16(7):435-44

Do statins prevent AD?

Do they help in treatment of AD?

What do statins do

- Beneficial changes to lipid profiles.
  - ↓ cholesterol
  - ↓ LDL
- Affect other serum and cell markers
  - Anti-oxidant
  - Anti-inflamatory
  - Endothelial actions
  - ↓Aß in plasma and CSF in dose dependent

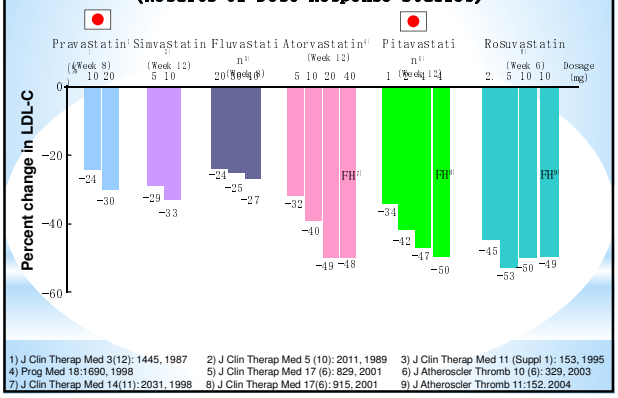
Current indications of statins

- Primary MI Prevention
- Primary MI Prevention in DM
- Secondary MI prevention
- Risk reduction CV events in perioperative period of cardiac revascularization procedures.
- Cholesterol Level Reduction in Familial Hypercholesterolemia Syndromes

What do statins do: Mechanisms affecting neurodegeneration

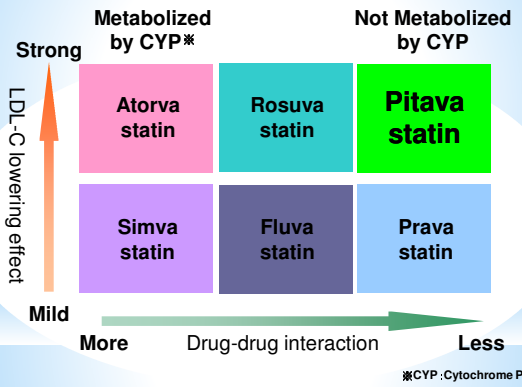
- Statins may have pleiotropic mechanisms:
  - Increase nitrous oxide production
  - Improve endothelial function
  - Decrease pro-inflammatory cytokines
  - Reduce expression of adhesion molecules on vascular walls
  - Reduce progression of atherosclerosis
  - Plaque stabilization
  - Reduce stroke risk

Effects of statins on LDL-C levels (Results of Dose Response Studies)



1) J Clin Therap Med 3(12): 1445, 1987
2) J Clin Therap Med 5 (10): 2011, 1989
3) J Clin Therap Med 11 (Suppl 1): 153, 1995
4) Prog Med 18:1690, 1998
5) J Clin Therap Med 17 (6): 829, 2001
6) J Atheroscler Thromb 10 (6): 329, 2003
7) J Clin Therap Med 14(11):2031, 1998
8) J Clin Therap Med 17(6):915, 2001
9) J Atheroscler Thromb 11:152. 2004

Characteristics of Statins

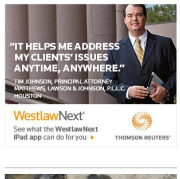


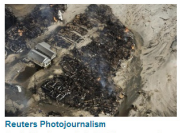
Statin and dementia

Epidemiology studies

Statins, new onset diabetes, memory impairment ?

ARTICLE COMMENTS (10)





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FDA adds diabetes, memory loss warnings to statins

2,305 個人都按讚這。註冊會成為朋友第一個個於人。

By Bill Berkrot and Ransdell Pierson
Tue Feb 28, 2012 5:29pm EST

(Reuters) - Health regulators are adding warnings to the labels of widely used cholesterol lowering drugs, such as Lipitor, to say they may raise levels of blood sugar and could cause memory loss.

The Food and Drug Administration announced on Tuesday the changes to the safety information on the labels of statins such as Pfizer Inc's Lipitor, AstraZeneca's Crestor and Merck & Co's Zocor that are taken by tens of millions of people.

Statins have been shown to significantly reduce the risk of heart attack and heart disease, and the FDA said the new information should not scare people into stopping taking the drugs.

"The value of statins in preventing heart disease has been clearly established," Amy Egan, deputy director for safety in FDA's Division of Metabolism and Endocrinology Products, said in a statement. "Their benefit is indisputable, but they need to be taken with care and knowledge of their side effects."

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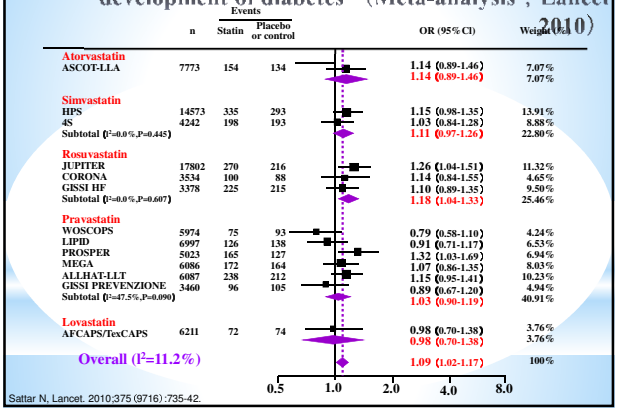
Association between different statins and development of diabetes （Meta-analysis ; Lancet 2010）



Sattar N, Lancet. 2010;375 (9716) :735-42.

Statins protective?

- Epidemiological studies → significantly reduced risk of AD/dementia
  - Rockwood 2002
    - Any LLAs ↓risk of AD (OR 0.25, 0.10-0.62)
    - Protective effect only in <80 years age
  - Jick et al 2000
  - Wolozin et al 2000: effect for lovastatin, pravastatin but not simvastatin
  - Yaffe et al 2002 – trend to protect against cognitive decline

Age-related association of cholesterol and dementia risk

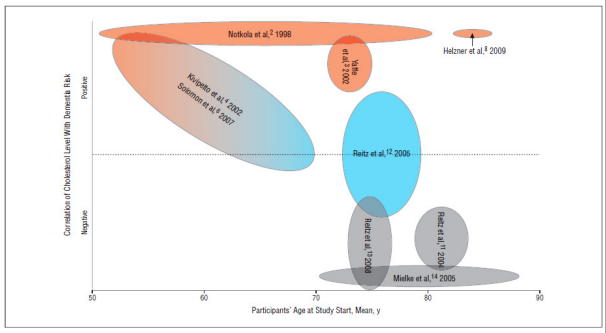


Figure. Relationship between outcome and age of participants in studies of the effect of cholesterol on dementia risk and progression. For each balloon, the left-most end is positioned at the mean age of participants at study start, the width represents the follow-up time, and the height indicates the cohort size. Red signifies a positive correlation of cholesterol level with dementia risk, gray a negative correlation, and blue no correlation. An additional study by Whitmer and colleagues' is excluded because the large size of its cohort and long follow-up period would have distorted the figure.

Shepardson NE et al., Arch Neurol. 2011;68(10):1239-1244

Cholesterol is essential for normal cellular functions

- Within the brain, most cholesterol is located in the plasma membrane and in the specialized membrane of the myelin sheath.
- Accordingly, it plays an important role in neural functions mediated by membrane-bound molecules such as ion channels, enzymes, and receptors and transporters for neurotransmitters (Abad-Rodriguez et al., 2004; Fassbender et al., 2001; Hering et al., 2003; Mason, 1994).
- Moreover, it has long been implicated in remyelination and neurite extension during neuron regeneration (Ong et al., 2003; Poirier, 2003; Thiele et al., 2000).

Cholesterol deficiency

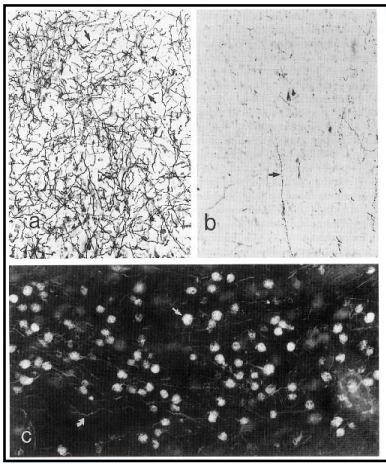
- According to the American Heart Association in 1994, only total cholesterol levels below 160 mg/dL or 4.1 mmol/l are to be classified as "hypocholesterolemia".
- A study of 121 healthy young women found that those with low cholesterol levels - below 160mg/dl - were more likely to score high on measures of depression and anxiety than women with normal or high cholesterol levels. Normal cholesterol levels are considered to fall within the range of 180mg/dl to 200mg/dl.
- low cholesterol is a potential predictor for depression and anxiety in certain individuals.

- Psychosomatic Medicine, May 1999

* Twenty-six-year change in total cholesterol levels and incident dementia: the Honolulu-Asia Aging Study

* Cholesterol levels in men with dementia and, in particular, those with Alzheimer disease had declined at least 15 years before the diagnosis and remained lower than cholesterol levels in men without dementia throughout that period.
* The difference in slopes was robust to adjustment for potential confounding factors, including vascular risk factors, weight change, alcohol intake, and use of lipid-lowering agents.

Steward R et al., Arch Neurol. 2007 Jan;64(1):103-7.



a. 正常 (Normal)

b. 失智 (Dementia)
1. Lost of cortical cholingergic innervation in AD.
2. Middle temporal gyrus

c. 失智 (Dementia)
1. Nucleus Basalis
2. NFTs

* Cholesterol deficiency and neurodegenerative disorders

* Shortage of cholesterol affects the function of brain cells and has been implicated in the pathogenesis of several neurodegenerative disorders.
* Cholesterol deficiency
  * impairs synaptic plasticity
  * induces tau hyperphosphorylation and facilitates the formation of paired helical filament in neurofibrillary tangles, one of the hallmarks of Alzheimer's disease (AD)

* (Abad-Rodriguez et al., 2004; Fan et al., 2001; Koudinov and Koudinova, 2001; Mauch et al., 2001).

* Cholesterol deficiency and neurodegenerative disorders

* Several studies have reported a reduced level of cellular cholesterol in AD brain and in the mouse model for AD, partly owing to oligomeric amyloid β-protein (Aβ) causing lipid leakage from neural cells

* (Mason, 1994; Michikawa et al., 2001; Molander-Melin et al., 2005; Roher et al., 2002; Svennerholm and Gottfries, 1994; Yao and Papadopoulos, 2002).

* Better memory functioning associated with higher total and LDL cholesterol levels in very elderly subjects without the APOE4 allele

* High total cholesterol and high LDL cholesterol were associated with higher memory scores for non-carriers of the APOE4 allele.
* No significant associations between cognitive performance and lipid profile were found for carriers of the APOE4 allele.

Rebecca W et al., Am J Geriatr Psychiatry. 2008; 16(9): 781–785

* Take home massage

* Midlife total cholesterol is an independent risk factor for AD.
* Epidemiological studies indicate that patients receiving statins for a long period have a reduced risk of dementia.
* Lower cholesterol level in age>75 y/o group may potentially increased the incidence of new onset diabetes as well as of dementia.