history, possible de novo mutations should be sought in families with sporadic cases by genetic testing, thus requiring appropriate genetic counselling procedures.

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References

- 1 **Laplanche JL**, El Hachimi KH, Durieux I, *et al.* Prominent psychiatric features and early onset in an inherited prion disease with a new insertional mutation in the prion protein gene. *Brain* 1999;122:2375–86.
- 2 **Croes EA**, Theuns J, Houwing-Duistermaat JJ, *et al.* Octapeptide repeat insertions in the prion protein gene and early onset dementia. *J Neurol Neurosurg Psychiatry* 2004;75:1166–70.
- 3 **Beck G**, Kawano T, Naba I, *et al.* A case with a 120 base pair insertional mutation in the prion protein gene the first case in Japan. *J Neurol Neurosurg Psychiatry* 2005;76:756–8.

- 4 **Goldfarb LG**, Brown P, McCombie WR, *et al.* Transmissible familial Creutzfeldt-Jakob disease associated with five, seven, and eight extra octapeptide coding repeats in the PRNP gene. *Proc Natl Acad Sci USA* 1991;88:10926–30.
- 5 Origin of extra prion repeat unit (online). Available at: http://www.mad-cow.org/prion_repeat_insertion.html (accessed 19 September 2007).

Attenuation of Kernig's sign by concomitant hemiparesis: forgotten aspects of a well known clinical test

The precise neurological evaluation of patients with a depressed level of consciousness may present a challenge, even for experienced neurologists. Meningeal signs, particularly Kernig's sign and neck stiffness, are helpful in suggesting the diagnosis of meningeal irritation in intracranial infections, oedema or haemorrhage and belong to the limited number of physical signs examined in patients with coma or altered mental status. As long ago as 1907, the German-Russian physician Vladimir Kernig noticed an attenuation of his "Kernig's leg sign" on the paretic side in patients with meningeal irritation and concomitant hemiparesis.¹ The American neurologist Thorner described in 1948 a modification of various meningeal signs on the paretic side.² According to Thorner, Kernig's sign as well as the rarer Brudzinski's sign can be both symmetric and asymmetric. In the case of asymmetric meningeal signs, hemiparesis on the side of less pronounced meningeal signs should be assumed. On the contrary, meningeal signs should always be symmetric in meningitis and subarachnoid haemorrhage without parenchymal involvement and paresis.² Thorner pointed to an attenuation of meningeal signs on the paretic side as a very quick and easy method of diagnosing unilateral motor deficits.³ Diminution of Kernig's sign on the paretic side was explained by Thorner through disturbed transmission of a reflexive response to crural flexor muscles via the affected pyramidal tract.²

Both Kernig's hint in his historical publication and Thorner's subsequent study remained unknown and nowadays seem to be completely forgotten.

The aim of this study was to evaluate the diagnostic usefulness of an asymmetric Kernig's sign as an indicator of the presence of a hemiparesis in the clinical practice of critical care neurology.

Patients and methods

We examined 51 consecutive patients with a positive Kernig's sign and depressed level of consciousness: cerebral infarction $n = 1$; tumour $n = 1$; meningoencephalitis $n = 5$; cerebral haemorrhage $n = 14$; and meningitis $n = 30$. A CT or MRI scan was performed in all patients. Kernig's sign was examined bilaterally as follows: the hip and knee were flexed to a right angle and then an attempt was made to passively extend the knee. Kernig's sign was assessed as positive if complete knee extension was not possible because of tonic tension of the crural flexor muscles. A quantitative analysis of the so-called "Kernig's angle" (the angle between the upper and lower leg measured with a protractor) was performed in each patient. We considered Kernig's sign as positive when the "Kernig's angle" was $<180^\circ$.

Results

Asymmetry of Kernig's sign was found in all patients ($n = 21$) with meningeal irritation, who were found to have a concomitant hemiparesis or unilateral pyramidal signs, such as increased deep tendon reflexes, Babinski's sign, etc, and had corresponding cerebral lesions on CT/MRI (table 1). There were eight women and 13 men, aged 20–90 years. The angle of Kernig's sign was in direct proportion to the degree of paresis: the more pronounced paresis, the larger Kernig's angle (ie, the less pronounced Kernig's sign). In eight patients with hemiplegia, Kernig's sign was completely absent on the paretic side. Kernig's sign was symmetric in all patients ($n = 30$) with meningeal irritation without hemiparesis.

Table 1 Twenty one patients with a positive Kernig's sign and hemiparesis

Patient No	Diagnosis	State of consciousness	Hemiparesis	MRC score leg	Kernig's sign (left) (°)	Kernig's sign (right) (°)
1	Meningoencephalitis	Confusion	Right pyramidal signs	5/5	120	135
2	Left HS ICH	Somnolence	Right hemiparesis	3/5	120	160
3	Right HS ICH	Coma	Left hemiplegia	0/5	No	120
4	Right HS ICH	Coma	Left hemiplegia	0/5	No	135
5	Left HS ICH	Coma	Right hemiplegia	0/5	135	No
6	Right HS ICH	Sopor	Left hemiplegia	0/5	No	120
7	Left HS ICH	Sopor	Right hemiparesis	4+/5	120	135
8	Left ICH	Somnolence	Right hemiparesis	2/5	135	170
9	Right HS ICH	Somnolence	Left hemiparesis	4/5	145	120
10	Right HS ICH	Somnolence	Left hemiparesis	4/5	140	120
11	Meningoencephalitis	Confusion	Right pyramidal signs	5/5	120	130
12	Tumour (cerebral metastases)	Somnolence	Right hemiparesis	3/5	120	150
13	Right HS CI	Somnolence	Left hemiparesis	3/5	160	130
14	Meningoencephalitis	Sopor	Right pyramidal signs	5/5	100	110
15	Right HS ICH	Somnolence	Left hemiparesis	4/5	150	130
16	Left HS ICH	Somnolence	Right hemiparesis	3/5	120	160
17	Right HS ICH	Somnolence	Left hemiparesis	4/5	140	120
18	Meningoencephalitis	Confusion	Right hemiparesis	4+/5	110	130
19	Meningoencephalitis	Somnolence	Right hemiparesis	4/5	120	135
20	Left HS ICH	Sopor	Right hemiparesis	4/5	120*	140
21	Left HS ICH	Somnolence	Right hemiparesis	3/5	120	150

CI, cerebral infarction; HS, hemispheric ICH, intracerebral haemorrhage; MRC, Medical Research Council.

Discussion

Kernig's sign is the most common and, apart from nuchal rigidity, the only quantifiable sign of meningeal irritation.³ Kernig's sign is sometimes interpreted as positive when the knee cannot be extended beyond 135°. We considered Kernig's sign as positive in accordance with the opinion of its inventor (ie, if "Kernig's angle" was <180°).¹ It is known that Kernig himself let patients sit upright in order to elicit the sign later named after him and interpreted the test as positive if this resulted in immediate insuperable knee flexion.¹ Nevertheless, Kernig's original method was not used in this study, but the passive knee extension after initial hip and knee flexion to a right angle was carried out. This technique allows a more precise testing of Kernig's sign and is appropriated worldwide.^{4,5}

The present study confirms the results of Thorner's forgotten paper from 1948.² In addition to Thorner, who only noted attenuation of Kernig's sign by concomitant hemiparesis without performing any quantification, the quantitative evaluation of Kernig's sign was carried out in the present study. This revealed that the "Kernig's angle" was in direct proportion to the degree of paresis: the more pronounced the paresis, the larger Kernig's angle (ie, the less pronounced Kernig's sign). Moreover, the present study showed that a quantitative analysis of Kernig's sign may be quite a differentiated clinical test, which allows more detailed evaluation of motor deficits than the Glasgow Coma Scale or the FOUR score. For instance, in patient Nos 1, 11 and 14, who had unilateral pyramidal signs without clear evidence of paresis, Kernig's sign was slightly less prominent on the affected side than on the non-affected side (135° vs 120°, 130° vs 120°, and 110° vs 100°, respectively) (table 1). In patient Nos 3–6 with hemiplegia, Kernig's sign was diagnosed exclusively on the non-paretic side, suggesting that a strictly unilateral Kernig's sign should point to a hemiplegia or a leg plegia. In patient Nos 2 (Medical Research Council (MRC) score 3) and 8 (MRC score 2) with pronounced paresis, Kernig's sign was only minimally positive on the paretic side showing an angle of 160° and 170°, respectively, which, according to Kernig, corresponded to a weak degree of contracture (>150°).¹ We found no correlation between the degree of Kernig's sign and the level of consciousness, whereas patients with deep areflexic coma were not included in our study because of absent meningeal signs.

Although the clinical relevance of an asymmetric Kernig's sign is limited to patients with coma or altered mental status, in intracranial haemorrhage, meningoencephalitis, etc, its diagnostic value should not be underestimated. An asymmetric Kernig's sign is certainly of purely phenomenological interest in completely conscious patients with meningeal irritation and paresis because hemiparesis in these patients can be better scored on a motor scale such as the MRC score. However, unilateral attenuation of Kernig's sign can be applied in everyday clinical practice of critical care neurology as a reliable indicator of hemiparesis.

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References

- 1 Kernig W. Ueber die Beugekontraktur im Kniegelenk bei Meningitis. *Ztschr f Klin Med* 1907;64:19–69.
- 2 Thorner MW. Modification of meningeal signs by concomitant hemiparesis. *Arch Neurol Psychiatr* 1948;59:485–95.
- 3 Levy M, Wong E, Fried D. Diseases mimic meningitis. Analysis of 650 lumbar punctures. *Clin Pediatr (Phila)* 1990;29:254–5, 258–61.
- 4 Campbell WW. *DeJong's the neurologic examination*, 6th edn. Philadelphia: Lippincott, Williams & Wilkins, 2005:617–20.
- 5 Triumfov AV. *Local diagnosis in neurological diseases*, 15th edn. Moskau: MED press-inform, 2007:242–3.

Ataxic variant of Alzheimer's disease caused by Pro117Ala PSEN1 mutation

Presenilin 1 (PSEN1) mutations account for the majority of cases of autosomal dominant early onset Alzheimer's disease (AEOAD).^{1,2} The *PSEN1* gene encodes for a 467 amino acid transmembrane protein which functions as a subunit of the γ -secretase complex that cleaves amyloid precursor protein to generate the A β amyloid peptide. More than 160 different mutations have been reported (www.molgen.ua.ac.be/ADMutations) with a great diversity of phenotypes: very early age of onset, early myoclonus seizures, parkinsonism, spastic paraplegia associated with "cotton wool plaques" or rare frontotemporal variant of AD. Ataxia has been rarely described during the course of AEOAD caused by *PSEN1* mutations. Ataxia and psychiatric signs were recently reported as initial symptoms associated with a *PSEN1* Ser170Phe mutation.³ We report three patients from the same family with early prominent severe ataxia associated with dementia caused by a novel *PSEN1* mutation.

Case report

Patient III2

A 35-year-old woman (fig 1) was seen for writing and balance difficulties, with memory complaints. All three symptoms occurred contemporaneously 1 year previously. Examination showed severe ataxia with instability, marked dysarthria and dysmetria with intention tremor, brisk reflexes and rare myoclonus. Neuropsychological assessment, including Mini Mental Scale (score 22/30), Grober and Buschke Learning Test (GBVLT) (delayed total recall 5/16), Digits Backwards (3), Backward Spatial Span (3), Trail Making Test Task A (time 104 s) and B (= 191 s), Rey-Osterrieth Complex Figure Copy (18/36) and 2 min category fluency task (n = 13 animals) yielded abnormal performances. Cerebral MRI revealed mild cortical atrophy. CSF examination, including 14.3.3 protein analysis, was normal. CSF amyloid β (A β) levels were not investigated. EEG detected sporadic bilateral generalised spikes and waves that were asymptomatic. Spinocerebellar ataxias types 1, 2, 3, 6, 7 and 17, and dentato-rubro-pallido-luysian atrophy were excluded. Sequence analysis of the prion protein gene was normal. Two years later the patient was completely dependent,

with worsening of balance difficulties and falls twice per month. Cognitive state had deteriorated, with severe GBVLT immediate recall impairment (2/16), severe visuoconstructive deficit (Rey figure copy 6/36) and reduced verbal fluency (six animals in 2 min).

A second MRI showed a diffuse cerebral atrophy, and Tc-99m HMPAO SPECT found hypoperfusion in the associated parietal area without cerebellar hypoperfusion.

Patient II2

At age 29 years, the father of patient III2 (fig 1) had developed cerebellar signs with head tremor associated with upper limb extremities intention tremor, dysarthria and gait difficulties. Examination at age 32 years displayed cerebellar signs with dysmetria, gait ataxia and left Babinski sign. EEG, CSF study and fractionated gas encephalography were normal. Examination at age 35 years demonstrated severe axial and four limb ataxia, dysarthria and pyramidal signs with hyperreflexia and lower limb spasticity. Impairment of short term and long term memory was noted but no neuropsychological test was performed. Cerebral tomodensitometry was normal. Patient status worsened rapidly and he died a few months later. Autopsy was not done.

Patient I1

Patient II2's mother complained of gait instability from the age of 24 years (fig 1). Examination revealed gait ataxia and balance impairment with wide based gait, four limb dysmetria and dysarthria. Subsequently, memory deterioration appeared as well as pyramidal signs. Cerebellar signs and cognitive impairment progressively worsened and the patient was then lost to follow up. She died at age 35 years.

Genomic DNA was isolated from blood lymphocytes of patient III2 and her mother I1 after informed consent was obtained. The entire coding sequence and the exon/intron boundaries of the *PSEN1* gene were sequenced, as previously described.⁴ To ensure that mutations detected in patients were not common polymorphisms, we determined that they were absent in 50 control DNA samples.

One novel *PSEN1* mutation was found in patient III2. She was heterozygous for the c349 C>G pPro117Ala mutation in exon 5 and for the known polymorphism c953 A>G pGlu318Gly in exon 9. No *PSEN1* mutation was found in I1. This was consistent with the

Figure 1 Family pedigree. Squares = males; circles = females; filled symbols = affected subjects; diagonal line = deceased subject; arrow = proband. ND, sequencing not done. Age of onset, current age or age at death (in parentheses) are indicated.