Pathophysiology of Cerebellar Dysfunction in the Wernicke-Korsakoff Syndrome

Roger F. Butterworth

ABSTRACT: Cerebellar ataxia is a common presenting sign in the Wernicke-Korsakoff syndrome (WKS). Recovery from ataxia following thiamine treatment is rarely complete, suggesting the existence of both a reversible ("biochemical") lesion as well as irreversible, neuropathological damage. Cerebellar pathology in WKS includes severe loss of Purkinje cells in superior cerebellar vermis as well as neuronal loss from the granular layer. In addition, damage to inferior olivary nucleus could result in loss of climbing fibre input to cerebellum in this condition. Experiments using an animal model of WKS, the pyrithiamine-treated rat, reveal selective reversible decreases of α-ketoglutarate dehydrogenase (αKGDH) in cerebellum. Decreased enzyme activities are associated with decreased cerebellar content of GABA and aspartate. Thiamine reversal of neurological symptoms results in normalization of cerebellar enzyme activities and GABA content suggesting that reduced activities of αKGDH constitute "the biochemical lesion" in these animals. Possible mechanisms implicated in neuronal cell death in cerebellum include impaired cellular energy metabolism, focal lactic acidosis and excitotoxic damage resulting from excess glutamate release mediated by N-methyl-D-aspartate (NMDA) receptors. Similar mechanisms could be involved in the reversible and irreversible neurological symptoms of WKS in humans.

RESUME: Pathophysiologie de la dysfonction cérébelleuse dans le syndrome de Wernicke-Korsakoff. L'ataxie cérébelleuse est un mode de présentation fréquent du syndrome de Wernicke-Korsakoff (SWK). La récupération est rarement complète suite au traitement par la thiamine, suggérant la co-existence d'une lésion réversible ("biochimique") et d'une lésion irréversible, un dommage neuropathologique. La pathologie cérébelleuse dans le SWK comprend une perte sèvère de cellules de Purkinje dans le vermis cérébelleux supérieur ainsi qu'une perte neuronale dans la couche granuleuse de l’écorce cérébelleuse. Dans cette affection, l’atteinte de l’olive inférieure peut amener une perte de l’influx provenant des fibres grimpantes vers le cervelet. Des études effectuées sur un modèle animal de SWK, le rat traité à la pyrithiamine, révèlent une diminution réversible sélective de l’α-kétyoglutarate déshydrérogenase (αKGDH) dans le cervelet. Des activités enzymatiques diminuées sont associées à une diminution du GABA et de l’aspartate dans le cervelet. Le soulagement des symptômes neurologiques par la thiamine amène une normalisation des activités enzymatiques cérébelleuses et du contenu en GABA, suggérant qu’une activité de l’αKGDH diminuée constitue la "lésion biochimique" chez ces animaux. Nous mentionnons l’atteinte du métabolisme énergétique cellulaire, une acidose lactique focale et un dommage excitotoxique résultant d’une libération excessive de glutamate par l’intermédiaire des récepteurs du N-méthyl-D-aspartate comme étant des mécanismes qui sont possiblement impliqués dans la mort des neurones cérébelleux. Des mécanismes semblables pourraient être impliqués dans la pathogénèse des symptômes neurologiques réversibles et irréversibles du SWK chez l’humain.

with little spare capacity of the system. The highest thiamine turnover rates occur in cerebellum (0.551 μg/g/h compared to 0.159 μg/g/h for cerebral cortex).1

**Recovery From Ataxia Following Thiamine Treatment of Patients With Wernicke’s Encephalopathy**

In the comprehensive study by Victor et al.,2 107 WKS patients with ataxia of stance or gait were studied both prior to and following thiamine treatment. Complete recovery from ataxia occurred in 41 patients (38 per cent); in most cases, improvement began within 2 - 6 days after the start of thiamine treatment. The time required for complete recovery in these patients varied from 1 - 8 months. 37 patients (35 per cent) showed wide-based gait ataxia in all cases. Improvements again started within one week and maximal recovery was noted after 2 - 7 months. In a further 29 patients (27 per cent), no significant improvement from ataxia was noted following thiamine treatment for periods of more than 2 months.

**Cerebellar Pathology in the Wernicke-Korsakoff Syndrome**

Degeneration of the cerebellar cortex was described by Victor et al.2 in 15 of 27 patients. The most striking change was a loss of Purkinje cells limited to the folia of the superior cerebellar vermis accompanied by an increase of Bergmann glia. In some cases there was also a partial loss of neurons from the granular layer, thinning of the molecular layer and concomitant astrocytic proliferation. It is generally presumed that the chronic ataxia of stance and gait results from lesions of the superior vermis.2 In 7 cases of alcoholic cerebellar degeneration in a group.4 Histological measurements of the area of the molecular layer varied in the degree of shrinkage between lobes and granular layers of the cerebellar vermis showed that the cerebellum of symptomatic pyrithiamine-treated rats is associated with increased alanine1 and lactate,10 consistent with decreased aKGDH, being a rate-limiting tricarboxylic acid cycle enzyme, is intimately involved in mitochondrial energy metabolism. Thus, reductions of aKGDH and decreased GABA synthesis most likely constitute “the biochemical lesion” in thiamine-deficiency encephalopathy. Extrapolation of these findings to WKS in humans suggests that thiamine reversal of ataxia is a consequence of normalization of defective aKGDH activities and GABA synthesis in cerebellum.

**Experimental Animal Model of WKS: the Pyrithiamine Treated Rat**

Pyrithiamine is a central thiamine antagonist. Daily treatment of rats with pyrithiamine results, within 2 weeks, in neurological symptoms and, ultimately, neuropathologic damage of a similar nature and distribution to that encountered in WKS in humans.6,7 Thus, neuropathologic lesions of mammalian bodies, thalamus, lateral vestibular nucleus, inferior olivary nucleus and cerebellum are observed in the brains of symptomatic pyrithiamine-treated rats.6

Daily administration of pyrithiamine to rats results in diminished central stores of thiamine and thiamine pyrophosphate (TPP), the enzyme cofactor form of the vitamin.8

### Cerebellar Pathology

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<tr>
<th>Table 1. Cerebellar Pathology in Alcohols With or Without WKS</th>
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<td>Cerebellar Wt. (g)</td>
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<td>alcohols without WKS (12)</td>
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* p < 0.05 compared to normals and alcohols without WKS (data from Phillips et al. 1990, reference 5)
synthesis and ensuing compromise of cellular energy metabolism. Measurement of high energy phosphates in the brains of symptomatic pyrithiamine-treated rats revealed decreases of ATP and phosphocreatine in brainstem of affected animals (Aikawa et al. 1984). Cerebellar high energy phosphates, on the other hand, were unchanged in these animals.

Increased brain lactate has consistently been observed in the brains of animals with thiamine deficiency and it has been suggested that focal accumulation of lactate and the consequent pH changes could be responsible for neuronal loss in this condition. In support of this possibility, a recent autoradiographic study using 14C-dimethylxazolinedione as pH marker, acidosis was observed in several brain regions including cerebellar cortex of symptomatic thiamine-deficient rats. Furthermore, treatment of thiamine-deficient animals with the Ca^2+ channel blocker nimodipine resulted in prevention of neurological symptoms and of acidosis in several brain structures of these animals, including cerebellum. It was suggested that pH changes were related to an improved ability of the brain to reduce its proton load in the presence of nimodipine.

Finally, there is evidence to suggest that neuronal cell death in thiamine deficiency may be the result of N-methyl-D-aspartate (NMDA) receptor-mediated excitotoxic damage. The nature of the tissue damage in thiamine deficiency resembles that observed following anoxic/ischemic insults suggesting the involvement of excitatory amino acids. In support of this contention, treatment of animals with the NMDA receptor antagonist MK-801 led to a marked reduction of lesions in medial geniculate and mammillary bodies in pyrithiamine-treated animals. Protective effects of NMDA receptor antagonists on
cerebellar damage have not been studied. Possible pathophysio-
logical mechanisms implicated in neuronal cell death in WKS
are shown schematically in Figure 3.

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