

# Hypomagnesemia and Transient Cerebral Ischemic Attacks (TIA)\*

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## Zusammenfassung

Es wird über 103 Tetaniepatienten mit transitorischen zerebralen ischämischen Attacken (TIA's) berichtet, die über einen Zeitraum bis zu 12 Jahren beobachtet wurden. Hypomagnesiämien kommen in dieser Gruppe signifikant häufiger vor als bei Normalpersonen. Beim Vergleich mit anderen TIA-Patientengruppen aus der Literatur fanden sich bei den Tetanikern mit TIA's drei wesentliche Unterschiede: jüngeres Manifestationsalter (34 Lebensjahre), Überwiegen der Frauen (88 %) und günstigere Prognose mit bisher nicht bekannten Herzinfarkten und letalen Ausgängen. — Die Prognose wird möglicherweise durch die hochdosierte Mg-Langzeitmedikation günstig beeinflusst.

## Summary

103 patients with a tetanic syndrome combined with transient cerebral ischemic attacks were observed over a period up to 12 years. In this group hypomagnesemia was significantly more frequent than in controls. In comparison with studies on unselected TIA-patients published in literature, three characteristic features are evident: lower age of manifestation (34 years on average), predominance of female sex (88 %) and a better prognosis (no myocardial infarction and no exitus letalis until now). — Evidence is given that the prognosis is influenced by highdosed Mg-longtime-medication.

## Résumé

103 malades avec l'association de tétanie et de AIT ont été suivis pendant une période allant jusqu'à 12 ans. Ce groupe présente une hypomagnésémie significative par rapport aux témoins. Ces tétaniques avec AIT se distinguent par 3 critères du groupe des AIT non tétanique: 1. âge moyen plus jeune (34 ans), 2. prédominance féminine (88 %), 3. meilleur pronostic (ni infarctus myocardique, ni mort). — Le pronostic favorablement est influencé par une magnésiothérapie au long cours.

## Introduction

A lot of studies have been carried through so far about the relations between myocardial infarction and magnesium supply, but, surprisingly, possible connections between magnesium and acute cerebral ischemia, which at least should be based on very similar pathophysiological mechanisms, have been practically neglected in literature.

Particularly *Altura* [1] and *Nguyen Duong* [18] have impressively illustrated in vitro the connections between contractility of blood vessels, among them those of brain, and extracellular Mg-concentrations: a decline of Mg-concentrations below 1.2 mmol/l leads to constrictions of heart and brain vessels, probably both through direct mechanisms in the smooth muscular system and indirectly through interactions with vasoconstrictory substances. On the other hand, by increasing extracellular Mg-concentrations, a reduction of vascular tone and contractility can be achieved.

With the exception of Finland and the United States [11] the incidence of strokes is increasing all over the world and has reached in the GDR now a figure of 20—30 per 10 000 inhabitants and year [4].

In a retrospective study indications of TIA have been found in about 50 % of apoplexy patients. In cases these neurological disturbances recede within 24 hours we speak of 'transient ischemic attacks/TIA'; if the period of remission is longer than one day they are called 'prolonged rever-

sible ischemic neurological deficits/PRIND'.

In 5—6 % of patients with TIA a complete stroke (CS) occurs within one year; after five years already in 50 %. About one third of those TIA-patients dies after 10 years and myocardial infarction as cause of death is indicated three times more frequently than apoplexy [12, 17, 19, 21, 22].

## Material and Methods

In 1976 we have drawn attention for the first time to the increased incidence of TIA in tetanic patients and reported at that time of about 26 such cases among a total patient population of 248 [6].

In the meantime the number of such TIA-patients cared for by us has grown to 103 and in some cases the period of observation extends already up to 12 years. We are now able to give more detailed informations about clinical and paraclinical peculiarities of this special form of spasmophilia. This TIA-group is taken from a total number of more than 1000 tetanic patients which have been cared for at our clinic, mostly over many years. A great part of them is from the Berlin region, but those cases particularly complicated and resistant to therapy are from all parts of the GDR. The clinical degree of severity is therefore high above the average, above all since not few patients had been transferred to us from other districts with the purpose to give a medical expert opinion with respect to invalidity.

\* Results presented at the 6<sup>th</sup> Hohenheimer Magnesium-Symposium, 24. 9. 1983

Differential-diagnostically not clear syndromes like disturbances of sensibility, memory and coordination as well as drop seizures and more global cerebral ischemia in the sense of circulatory collaps have been excluded from transient neurological deficits.

All TIA-patients have been neurologically examined several times depending on the symptoms and the course of illness. Hemodynamic informative non-invasive methods such as *Doppler-sonography*, *rheography*, *dynamic brain scintigraphy* as well as *electroencephalography* and *computer-assisted cranial tomography* have been applied, some times repeatedly; *angiographic investigations*, however, only with great caution.

Calcium was measured flame-photometrically, Magnesium by using the AAS-technique.

## Results

Frequency distributions of neurological deficits with the predominance of aphasic and neuroophthalmological disturbances remained unchanged over the years (table 1). Rare neurological deficits which have been observed in one patient only are not enlisted in table 1: *abducens-paresis*, *velum-paresis*, *paraparesis* and *spastic occlusion of eye-arteries*.

The portion of irreversible deficits remained almost constant in comparison with 1976: at that time the figure was 3 out of 26 patients, now 13 out of 103, in detail:

6 hemipareses (CS),  
5 sudden deafness,  
1 convergence paresis and  
1 velum paresis.

Up to now the diagnostic measures described haven't led in any case to an indication for a neurosurgical intervention, i.e. there were no intracranial tumors, malformations of brain

Table 1: Incidence of mostly transitory (TIA) and prolonged neurological deficits (PRIND) in 103 tetanic patients

neurological deficits	number of patients
aphasia	34
hemiparesis	29
diplopia	15
sudden deafness	13
monoparesis	11
hemianopsia	7
menière-disease	7
sensible disturbance in trigeminus-area	6
reduced visual fields	5
amaurotic attacks ambilateral	5
visual pareses	4
quadrantanopsia	3
amaurotic attacks unilateral	2
central scotoma ambilateral	2

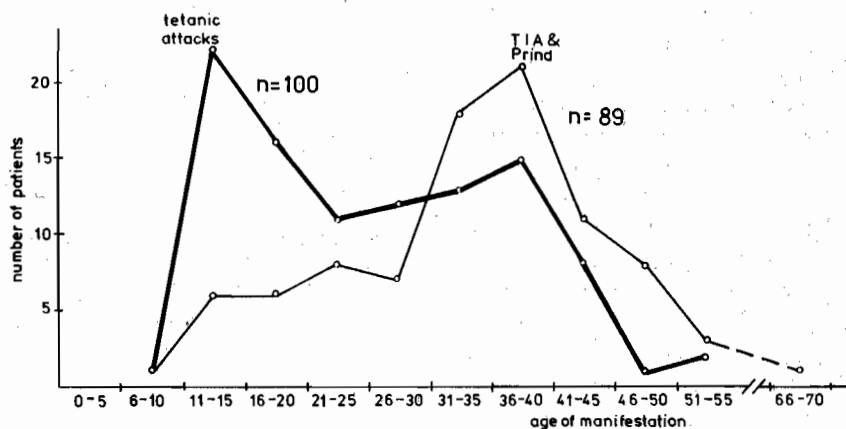


Fig. 1: Distribution of the first manifestations of tetanic fits and TIA

vessels etc. So far there has not been any incidence of myocardial infarction in any of these patients. Up to now there has not been any lethality among the 103 patients.

The average age of tetany manifestation defined on the basis of the incidence of the first fit is with 26.5 years of life, this is only very little below that of tetanic patients without TIA ( $n=103$ ), namely 27.8 years of life. Taking into consideration the distribution of frequency of tetany manifestation over the years of life and comparing them with an unselected group of tetanics — climax of manifestation here 30 years of life — the increased

incidence of early manifestations with a climax between the 11<sup>th</sup> and 15<sup>th</sup> year of life, however, attracts attention. An early manifestation correlates with an especially high degree of clinical severity [7].

On an average, only 7.5 years later the neurological deficits become manifest for the first time with a climax between the 36<sup>th</sup> and 40<sup>th</sup> year of life. Only in 5 patients (5.6%) TIA preceded the manifestation of tetany; in 20 patients the manifestation of tetany and TIA were almost synchronous (Fig. 1).

Comparing the clinical characteristics of tetanic patients with and without TIA some special

features are apparent (table 2): The distribution of sexes is almost equal in the two groups. (In unselected TIA-populations the male sex dominates.) Hyperventilation attacks occur in slightly increased frequency in the TIA-group. The pronounced degree of clinical severity of this group is obvious from the frequency of epileptic fits, most particularly from premature invalidity. The average age for receiving an invalidity pension is around the 40<sup>th</sup> year of life.

The portion of reduced concentrations of potassium, calcium and magnesium was almost the same in the two groups of tetany (table 3). Hypocalcemia occurred somewhat more rarely in the TIA-group, but the difference of the arithmetic average was not significant.

The incidence of hypomagnesemia in the TIA-group is significantly higher than in controls (table 4). Comparing the relative frequencies of Mg-concentrations between tetanics with and without TIA the former show a slight shift towards the left in the graph (Fig. 2) which however didn't reach the level of significance.

## Discussion

In comparison with big unselected TIA-populations reported in literature [4, 12, 17, 19, 21, 22] the following characteristics are imposing in our group: (a) an earlier age of manifestation, (b) a reversed distribution of sexes and (c) an essentially better prognosis pro ad sanationem, i.e. a much lower rate of CS and pro ad vitam, the latter being conditioned among other things also by the complete lack so far of myocardial infarction.

From the enormous variety of potentially pathogenic factors of TIA in tetanic patients only a few number can be discussed: In our TIA-group there is a relatively much lower incidence of negative prognostic factors such

Table 2: Comparison of clinical features in tetanic patients with and without TIA

	with TIA			without TIA		
	total number	frequency abs.	rel.	total number	frequency abs.	rel.
female sex	103	91	88.3 %	187	161	86 %
hyperventilation	102	77	75 %	190	131	69 %
epileptic fits	103	11	10.7 %	149	8	5 %
untimely invalidity	103	21	20.4 %	133	7	5.3 %

Table 3: Percentage of lowered electrolyte concentrations in tetanic patients with and without TIA <sup>1)</sup>

	with TIA			without TIA		
	total number	frequency abs.	rel.	total number	frequency abs.	rel.
hypopotassemia $\leq 1.95$ mmol/l	50	9	18.0 %	61	10	16.4 %
hypocalcemia $\leq 2.25$ mmol/l	66	16	24.2 %	82	24	29.3 %
hypomagnesemia $\leq 0.70$ mmol/l	64	19	29.7 %	67	20	30 %

<sup>1)</sup> 1—2 (3) blood-samples for each untreated patient.

Table 4: Frequency of hypomagnesemia ( $Mg \leq 0.7$  mmol/l) in controls and tetanic patients with or without TIA

	number of estimations	number of hypomagnesemia	percentage of estimations	significance <sup>1)</sup>
controls (n = 46)	119	5	4.2	p < 0.01 n.s.
patients with TIA (n = 66)	96	22	22.9	
patients without TIA (n = 67)	177	28	15.8	

<sup>1)</sup> Chi<sup>2</sup> — Test

as high blood pressure, diabetes mellitus and coronary heart diseases than in unselected TIA-patients. Thus we can assume that in TIA with tetanic syndrome more functional factors are important involving several systems and pathways which have, however, in common the final consequence: a breakdown of energy metabolism and supply in the corresponding brain area. In this connection we have discussed some data and

hypotheses in this Journal three years ago [8].

Here some pathophysiological mechanisms shall be summarized which may be important both for tetany, especially hyperventilation tetany, and for this type of TIA. The key of the problem seem to be membrane conditions. In case of hypomagnesemia an impairment of the active electrolyte exchange will result due to reduced activity of membrane-bound, Mg-dependent,

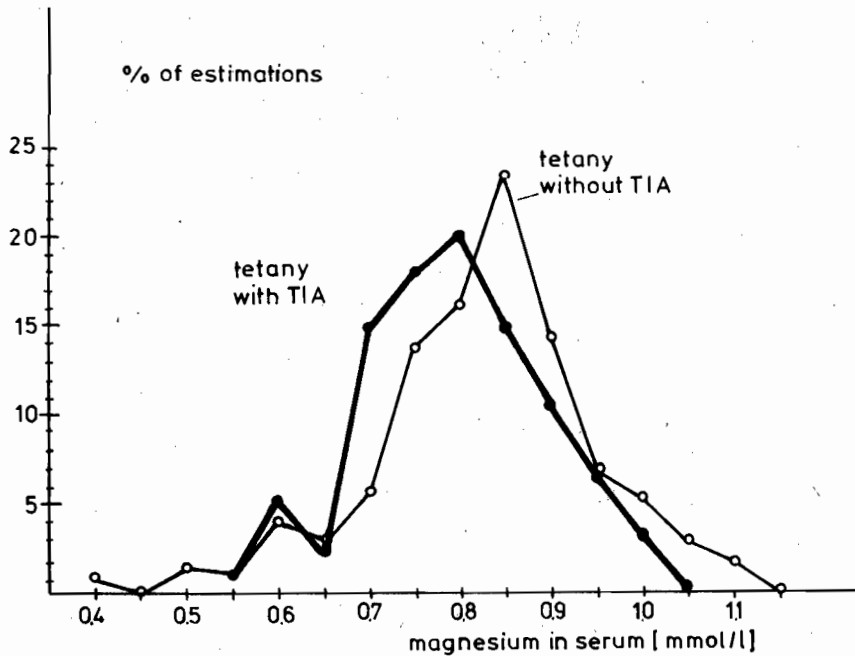


Fig. 2: Frequency of Mg-concentrations in untreated tetanic patients with and without TIA

Na-activated ATPase. As a consequence there is a stereotype alteration of electrolyte gradients with intracellular Ca-, Na- and water accumulation and Mg- and K-depletion [7, 10, 15]. The intracellular Mg-depletion disturbs the energy storage (Mg-ATP-complexes) enhancing mitochondrial respiration. But the increased intracellular calcium is known as an uncoupler of oxidative phosphorylation. The resulting lack of intracellular oxygen induces a switch to more anaerobic glycolysis due to the Pasteur-mechanism [9, 23].

From the vascular side, the oxygen and substrate supply can be reduced by vasospasms especially in the brainstem (via hypomagnesemia and hypocapnia — [14]). Hypocapnia may, in addition, lead to the Bohr-effect with the diminution of oxygen shift into the tissue, to a decrease of blood pressure via dilatation of splanchnic vessels [20]. Further effects of hypocapnia are a decrease of plasma volume and an increase of blood viscosity due to a shift of plasma water into tissues [20].

The high incidence of mitral valve prolapse (MVP) in tetanic

patients [3] with the elevated risk of microembolism [2, 13] is a further potential factor in the pathogenesis of TIA within the tetanic syndrome. An answer must be found to the question, whether MVP is more frequent in tetanics with TIA than in tetanic patients without this dangerous cerebral complication.

The list of possible pathogenetic factors is very simplified and not complete but it shows that the frequent combination of tetany and TIA is not accidental.

Despite so many problems not yet solved we can draw two conclusions for clinical praxis:

- It is possible that there are connections not only between declining Mg-supply and the increasing rate of myocardial infarction, but also with the growing rate of strokes.
- The lack of myocardial infarction so far in our TIA-group and the comparably very low rate of CS after a long period of observation has possibly to be associated with the consistently implemented long-time oral medication of magnesium in high doses between 300—700 mg Mg/d.

Since this medication has proved to be practically free of risk, one should generally recommend, already at this stage of scientific findings, the use of high dosed oral Mg-preparations with unselected TIA-patients and corresponding risk groups, of course together with well tried medicamentous strategies like thrombocyte aggregation blockers and last not least attentive medical care to be provided to this group of persons which is highly endangered.

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