REVIEW

Myalgic Encephalomyelitis: Guidelines for Doctors

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HISTORY

For those of us who are involved in the care of patients with this condition, the recorded work of Biorn Signurdsson (1913-1953) in connection with the Akureyn outbreak in Iceland which affected over 1000 patients, both children and adults was repeated by Melvin Ramsay when he was involved in the outbreak in his hospital which became known as the "Royal Free Disease" but defined by him as Myalgic Encephalomyelitis. This was followed by an excellent monograph in 1969 by Luis Leon-Sotomayor published by Pageant Press International Corp., New York and entitled, "Epidemic Diencephalomyelits; A Possible Cause of Neuropsychiatric, Cardiovascular and Endocrine Disorders." Since then many colleagues from the U.K. and other countries have demonstrated the pathological systemic consequences which may occur after a viral illness and have long term effects. All this work has been pursued by many colleagues in the U.K. and abroad since then, amongst whom are 72 who contributed to the book of more recent origin and published by the Nightingale Research Foundation, entitled, The Clinical and Scientific Basis of Myalgic Encephalomyelitis.

INITIATING ILLNESS

In the U.K. for 4-5 decades, we have found that an initial illness caused by one of the enteroviruses, was the most frequent cause of the ensuing illness known as M.E. These enteroviruses included the three polioviruses, the ECHO group and also the Coxsackie A and B groups. Unlike pesticides and other inorganic substances viruses can replicate and mutate hence there can be epidemic and endemic outbreaks. In other countries other viruses have been involved. In the U.K. the Epstein-Barr virus has been claimed as an initiating cause of this illness. However, in our work this has not occurred in epidemic or endemic forms as outlined here. The acute stage may have varying presentations which may be transient and mild, or severe and persistent. These presentations may be respiratory infections or cardiac infections (pericarditis, endocarditis or myocarditis) resulting in a

constrictive pericarditis or a cardiomyopathy. Not only so but Bornholm disease may occur with severe spasmodic pain in the chest simulating angina or abdominal pain simulating appendicitis, cholecystitis or pancreatitis. Other viral syndromes occur such as Meniere's syndrome, or the more sinister, viral meningitis. On the other hand, the condition may be a general illness defined by both patient and doctor as the "flu." In any of these conditions the prodromal infections may appear to abate but the patient does not "get better." This is only a very brief resume of a large number of cases, which have been seen and followed up for many years.

PATHOLOGICAL RESULTS

As with poliomyelitis, the symptoms in M.E. are somewhat diffused but do involve the nervous system. We should consider the terms applied to the effects of infection in the nervous system due to the poliovirus, which is the enterovirus. The term ANTERIOR POLIOMYELITIS referred to cases where the ANTERIOR horns of the spinal cord were chiefly affected. These neurons subserve EFFERENT outgoing neurological impulses. Hence the effects were on the "motor" system with some paralysis. The term POSTERIOR POLIOMYELITIS was also used to define lesions in the POSTERIOR horns of the spinal cord. These neurons subserve AFFERENT neurological impulses. The enteroviral groups to which we refer in these guidelines have been shown to have a propensity for, and cause the pathology in these AFFERENT impulse conducting neurons. Hence, the results are more noticeable to the patient than the doctor, which is not so with poliomyelitis. These pathological results may not be confined to the nervous system but may result in neurohormonal or other differing end organ effects. In CNS cases seen over 4-5 decades by one of us (Dr. John Richardson, MB BS) the computerized records, when analysed, reveal that the male cases with M.E. numbered 224 and females 469. From these figures it can be shown, that besides the female preponderance, the total number of varying CNS syndromes are greater for females as can be seen in the table. The viral etiology may be doubted by some, but if one remembers that the resulting CNS illness was accompanied in approximately 50% of both male and female patients with some other syndrome-ranging from cardiac, renal, pancreatic (with diabetes ensuing in some cases) to the more obscure thyroid or adrenal effects, then the possibility of a common etiological factor should not be ignored. Moreover, thousands of serological viral tests (including IgM, IgG and VP1) performed by us were positive and confirmed this relationship.

Certain CNS deformities also resulted in the offspring of mothers who had conceived whilst the serological tests were positive for enterovirus, prior to, or during pregnancy. In the first trimester these included agenesis of the septum lucidum resulting in blindness, agenesis of the corpus callosum, and also amyelination of white matter resulting in severe and diffuse lack of development. In viral infection in the late stages of pregnancy, fully developed organs were affected and we have shown cardiac effects such as

endocardial fibroelastosis (in two neonates), as well as brain damage in others. These cases have been recorded on MRI, videotape and, sadly, at autopsy. This diffuse variety of initiating and consequential illness is briefly reported here to show that we are not dealing with a simple, single entity, but with serious consequential illnesses. A summary of the CNS syndromes which followed an initial, serotype positive, viral infection is shown in the table next page.

Many other cases have come into this survey since this table was formulated, but the relative percentages in all aspects remained the same. The percentage of M.E. cases, compared to the total number of CNS cases is 42% for males and 46% for females showing that although the total numbers point to female preponderance in CNS illnesses, the percentage of M.E. cases is the same. Nowhere is a variety of systemic symptoms seen more often than in this syndrome. Whilst M.E. is a well defined entity, other associated organ pathology is not infrequent and can obscure the picture. In this series about 25% developed varying autosomal antibodies of which, for instance, antithyroid antibodies were found in 20% of cases studied. Thus much has been claimed by some to be purely psychiatric in origin, with labels ranging from simple depression to hysteria, and other vague hypotheses.

[Note: See table at http://www.co-cure.org/table.pdf]

PREVALENCE AND CLINICAL DIAGNOSIS

As shown, cases may be endemic, or present in sporadic clusters. They may follow an acute viral illness such as Bornholm disease, viral perimyocarditis, labyrinthinitis, or viral meningitis. A vague flu-like illness affecting the chest or bowels may be a harbinger of a more serious consequence. The malaise not only fails to recover, but becomes more defined, developing symptoms such as anosmia or marked concentration difficulties in a previously highly accomplished brain which cannot now recall a paragraph after reading it several times. Initially, muscle power may not appear to be affected but, if examined carefully, tender "softened spots" may be found in calf muscles and sometimes in the recti-abdomini. One such case had to have two operations for hernias which resulted from such "infarctions."

Muscle jitter will be found if carefully looked for in 25% of such cases. We find over the years that the history of the illness written by the patient is of enormous help and we have preserved these histories over four decades and the symptoms which were commonly reported in over 400 of these histories formed the basis of the Score chart which we in the Newcastle Research Group use. A score of 15 on this chart is highly suggestive of M.E.

A full and careful examination, as follows, is mandatory.

CHEST

This not only involves the lung fields but also careful attention should be given to heart sounds as a pericardial friction rub in some cases can be detected at the lower sternal border. This often signifies a pericarditis.

The blood pressure should be measured supine and then a tilt test performed, where the patient sits up at about 45 degrees. Labile recordings can be found in some cases and, no doubt, account for the reports of "fainting attacks when standing erect" and a few have fainted (see Score Chart). This labile blood pressure is usually considered to be due to neuro-vasomotor instability.

CENTRAL NERVOUS SYSTEM

Because the effects of this illness are primarily due to AFFERENT tracked pathology, examination must be related to this. In poliomyelitis and other syndromes primarily affecting the efferent pathways, attention to reflexes, etc., is appropriate but in these cases a more detailed approach is necessary to define the adverse signs resulting from the AFFERENT track involvement. Thus the 12 cranial nerves need to be considered first as certain abnormal sensations relating to the cranial nerves are found in these patients. These include abnormal response to olfaction (1st), varying abnormal optic responses (2nd, 3rd, 4th and 6th), facial/motor and sensory responses are through the trigeminal (5th) and the facial (7th) nerves, auditory (8th), valtal (10th). Afferent and efferent responses will be found.

[Note: See Newcastle Research Group M.E./CFS Score Chart at http://www.co-cure.org/chart.pdf .]

OLFACTORY (1ST)

A few cases suffer from anosmia, maybe due to involvement of the cortical olfactory centers rather than peripheral receptors.

OPTIC EXAMINATION

There may in some cases be paresis affecting the abducting eye muscles with diplopia on looking sideways. There may be saccadic movements which can be

recorded and these affect the reading of small print. In some cases there is a reversal of the Argyl-Robertson pupils, often seen in young patients, and this is often not noticed by the examining doctor. It is described in "Diagnosis of Nervous Diseases" by Purves Stewart and occurred in other cases of encephalitis. The pupils are dilated and do not respond to accommodation and also feebly to light. We have videoed these, with a control, often a parent, sitting next to the patient. The video recordings of these cases are retained. Occasionally the trochlear nerve is affected as its nucleus is situated in the midbrain area and this can be assessed by asking the patient to focus in a downward direction, when there is diplopia aggravated by looking sideways at the same time. The effects of light are more noticeable and many patients have to wear very dark glasses. This is NOT due to abnormalities in the receptor areas in the calcarine nuclei, but is due to midbrain "reading" of these visual images by forward projecting fibers from the calcarine nuclei. Eye movements should obviously be carefully assessed in all directions and any nystagmus, diplopia, oscillopsia or other abnormal signs noted. In this connection the excellent work done by Alfredo A. Sadun, MD, PhD (Doheny Eye Institute, California) confirms these observations (Last chapter, "Clinical and Scientific Basis of M.E./ CFS").

In a few cases such as hand-foot-and-mouth disease, the eyes can be affected and a marked conjunctivitis seen and videoed.

OPTIC FUNDI

Careful examination is essential. Whilst often they are relatively normal, in some a venous "cuffing" is seen, IF CAREFULLY LOOKED FOR. In some of these cases where MRIs have been performed unidentified objects (UBOs) have been noted and are considered to be due to such "cuffing" in the Virchow Robin spaces which contains CFS between the meningeal coating and cerebral blood vessels.

FACIAL EXAMINATION (7TH)

The three divisions of the facial nerve involve both motor and sensory sensations. In some cases lack of sensation may be found unilaterally in one discrete area and very occasionally some paresis. The latter has also been videotaped.

HEARING SENSITIVITY (8TH)

The Score Chart relates to this. Some modalities of sound, chiefly high

pitches, have very adverse, irritating effects. (This is also evident in animals.) The audiometer test is very helpful to assess and record the frequency and levels at which intolerance occurs.

VAGAL OUTFLOW (10TH)

This will be referred to in the section on bowel activity.

UPPER LIMBS

Apart from reflex and sensory activity, which should involve temperature, touch, vibration and two point discrimination, the pronator sign should be assessed. This involves the elevation of the arms above the head and, if positive, the palms will face outwards due to internal rotation of the whole limb with pronation of the forearm. This is also reported by Purves Stewart and was seen in chorea and other cases of encephalitis. This sign is not specific for M.E. and when it does occur it is not accompanied by the choreaform motions of the hands. A case referred recently as M.E. had a severe pronator sign accompanied by marked choreaform motions of the hands and had to be diagnosed as the new variant CJD-which was sadly proven later. Nevertheless this simple test should be performed and we have videotaped a number of cases.

The color the palmar surfaces of the hands should be noted in the acute stage, as the HFAM disease which occurs in some patients in the primary stages of the illness with conjunctivitis due to enteroviral infection, results in palmar erythematous changes.

ABDOMEN

Apart from the usual examination it is wise to do an ultrasound test. (A simple fetal monitor can be used.) Irritable Bowel Syndrome in our series occurs in approximately 20% of cases. We define this as the "boiling bowel syndrome" as it sounds like this on the sonic scan. Rory McCloy, BSc, MD, FRCS, in an excellent monograph described this and related this to the vagal pathways, both sympathetic and parasympathetic. He postulated that the trigger factors could be neuroneural or neuroendocrinal, resulting in the change of myoelectric activity from the normal 6 cycles to the faster 3 cycles per minute. Skin sensitivities occur and can be shown by scratching the abdominal skin where severe dermatographia can sometimes be seen, and again photographed, as we have done. A stated, palpitation of the abdominal recti for softened foci should NOT BE OVERLOOKED.

LOWER LIMBS

The usual check but care should be taken to note the reflex sensitivity as it can change. Blood flow can be assessed by palpation and ultrasound. The brainstem is "softened" in M.E. and any adverse effect, be it a RTA with whiplash injuries or rarely a LP can have unusual adverse effects with marked changes in the reflex activity. Thus the value of response should be noted initially and subsequently as, mild, moderate or severe. The Babinski response and joint position test, along with temperature, touch, and vibration tests should ALWAYS be done. In addition muscle jitter should be assessed. This is done by the examiner putting a hand on the patient's knee whilst seated on the examination couch and asking the patient to elevate the leg to the horizontal position and then slowly lower it. In some cases rapid jitter can easily be felt, seen and again videotaped. As with the upper limbs the temperature should be noted as in M.E. It is often much lower than normally would be expected.

STANCE

Walking ability relates to all modalities of locomotion, be it speed, toe-to-toe, or balance, etc. Romberg's should always be performed as the midbrain cerebellar connections are affected in a number of cases, but balance estimation is not confined to the Romberg test (with eyes closed) as it is impaired in the normal process of locomotion. This balance incoordination is frequently seen to be associated with the upper limb positive, pronator sign. Again it is not confined to M.E. but was seen and recorded in the patient with CJD. It presents itself as a rather spastic gait and, in M.E, the patient very often requires personal, or walking-stick support and often a wheelchair.

COGNITION, ETC.

It is not intended to discuss this in detail as the Score Chart and the patients own written histories will make this evident. Suffice to say that it can be verified by discussion. Moreover, if questioned many patients will recall very odd verbal and motor performances, e.g., forgetting words, or using incorrect words, or doing odd things such as, "putting the boiling kettle into the fridge." We find that they do not often mention the latter as they are so embarrassed, but, when sympathetically questioned, they relate these incidents with a raw smile! As shown by the Score Chart they find it difficult to talk or communicate with friends or relatives for long periods, apart from their sensitivity to sound, mentioned earlier. These various changes of activity are noted frequently by relatives as also the

periodic blanching of the face.

CLINICAL TESTS

If there is the slightest suspicion of myocardial involvement an ECG and if possible a 24 hour recording should be done. MRIs in some cases, if there is venous cuffing in the optic fundus may be interesting. The "Buspirone, Corticol/Prolactin test" is very helpful, as also the SPECT brain scans. Papers on these have been published in the Journal of Chronic Fatigue Syndrome, 1997-8.

Thorough serological tests should be done and involve routine blood counts, liver function tests, CPK and an autoimmune profile. Varying hormonal tests should be done if there is suspicion of end-organ dysfunction. A full viral screen should be mandatory and include the enteroviral groups and IgM and IgG and, if possible the VP1 test. An ESR should be done and repeated as necessary. In M.E. without other organ involvement it is usually normal. If raised it would indicate a non-specific inflammatory reaction, which requires further investigation. Tests for thyroid and adrenal function are helpful. However, care is needed as these can be attributed, if somewhat abnormal, to end-organ glandular failure rather than neurohormonal effects from the HPT or HPA axis.

In one case we had a patient who, following an illness with high titers to Coxsackie virus developed a mild proptosis, but had no goiter. This patient was seen by a junior hospital doctor and was inadvisably given carbimozole and, later when seen at home, was almost in a myxoedematous coma. Another recent case has been mistakenly diagnosed as Addison's disease. As with M.E. there are signs which are similar including weakness, fatigue and even orthostatic hypotension. However, in true Addison's disease there is diffuse tanning of both exposed and nonexposed areas, especially on points such as the elbows. Freckles occur on the forehead, face and neck as well as discoloration of the areola, lips, mouth, vagina and other mucous membranes. THIS DISCOLORATION DOES NOT OCCUR IN ADRENAL INSUFFIENCY
SECONDARY TO PITUITARY FAILURE WHICH IS A RESULT OF THE HPA AXIS SYNDROME.
In this patient and others we have seen there is, if anything, a blanching of the skin and a remarkable lack of pigmentation. To distinguish between failure due to hypothalamic or pituitary stimuli, a test using corticotrophin-releasing hormone (CRH) is useful. Patients with hypothalamic failure DO respond, whereas those with pituitary failure do not. This test should be done, but once again the clinical signs serve to differentiate between true Addison's disease and HPA axis.

PSYCHIATRIC TESTING

The Hamilton ratio score chart is useful but M.E. is not primarily a psychiatric illness and to label it thus just adds to the patients distress and has had devastating results. However, as with any such illness there are obviously feelings of oppression and frustration and a desire to "try anything that would help." Many psychiatrists recognize this and show sympathy which is very supportive. After all TLC is the best medicine available in many other illnesses

TREATMENT

The profuse range of treatments which have been advocated are described in the book, The Clinical and Scientific Basis of Myalgic Encephalomyelitis Chronic Fatigue Syndrome. However, as with anterior poliomyelitis the variety of treatments which have been tried, reflect the primary difficulty, and the old aphorism remains - "Sublata Causa Tollitur Effectus," which is "Remove the cause and the effect will cease." As can be demonstrated in cases who have succumbed to the poliovirus, this aphorism is not always true, for there are some effects which remain after the infection has ceased. Thus, whilst it is desirable to remove the CAUSE, to address the effects is a challenge in M.E. as it was in poliomyelitis. Some of the treatments which are used are as follows:

l. IgG Infusions have been used extensively both in the U.K. and abroad and the basis for this is considered to be the abnormal, cellular and humoral immunity in these patients. Replacement therapy with IgG is given to restore normal homoral immune function. Some clinicians use the I.V. infusions but we for many years have used I.M. injections. Professor R. Loria in personal communications has demonstrated the vortex of effects which occur when IgG is given I.M. rather than I.V. and thus it has more effective results. Also, instead of large amounts at extended intervals, we find that on average about 500 mg weekly has a "smoother" and more beneficial effect. However, before this therapy is given it is wise to do the serological tests alluded to earlier and show these to be positive.

The protective benefits may be seen by referring to the outcome in pregnancy. Over the years out of 249 female patients with high positive titers to a Coxsackie virus, 66 became pregnant. Forty-five of these (68.2%) had normal babies but the remaining 21 (31.8%) had abnormal babies. It is significant that for varying reasons, none of the mothers who had the abnormal babies had been protected by IgG infusions, but more than 90% of the remainder received IgG before and during pregnancy. (The records are retained.)

2. Ampligen. Robert Suhadolnik gave a good resume of this therapy. The immune changes he postulated might involve alterations in the 2-5A synthetase/Rnase L pathway. These changes have to be evaluated before the therapy is given. Ampligen is a biological response modifier which augments natural killer (NK) cell activity. It should be available in U.K. shortly on a named patient basis, but as shown here, it should only be used if the RNase investigations are positive and this is usually in the early stages of the illness.

3. Transfer Factor. Professor Hugh Fudenberg has done work on this and bases the treatment on its effects on immune dysfunction. TF is a dialyzable component of leukocytes and is capable of transferring delayed type hypersensitivity and has been used where there was a defect in cell-mediated immunity.

4. Efamol is an essential fatty acid (EFA). In M.E. one result may be a lowering of normal proportions of arachidonic acid and a reversal of the normal serum ratio of linoleic and oleic acids. These EFAs are necessary for normal cell membrane metabolism. Treatment with EFAs such as Efamol is postulated to help correct any such abnormality in this chain reaction. Details for these treatments are given in chapters in Byron Hyde's book.

5. Elagen. A large amount of scientific work has been done on this and it is basically an adaptogen and is considered to stimulate the normal activity of the immune system in response to physiological stress.

6. Thymic Hormones. Nathan Trainin's chapter in the Book summates the effect of thymic hormones and states that "viral antibody responses in vivo are thymus-dependent and therefore require the cooperation of viral antigen-specific helper T-cells." Thymic humoral factor gamma 2 (THF y2) was used. This is a very helpful chapter to read.

7. Alanthamine Hydrobromide. Galanthamine has been used by Snorrason et al. in Iceland. This was used because of the cholinergic defects which have been shown to occur in patients with M.E. In this connection, choline dihydrogen citrate with vitamin C has been used by J.R. for 4 decades-see attached notes. No adverse side-effects have been reported and very beneficial results have been demonstrated and noted by the patients.

8. Cognitive Therapy. Varying exercise techniques and other supportive treatments, which are too diffuse to specify have been given to help patients. These do not address the physiological cause or consequences of the illness. Unfortunately, in our experience over the years, both cognitive therapy and some other aspects of psychotherapy may have adverse effects because the patients sometimes feel that the responsibility for

succumbing to the illness is being laid upon them and that the responsibility for recovery lies within their own remit. Maybe those of us actively involved in seeing patients are aware that we also have the opportunity to empathise and give support without making undue demands or suggesting that the "patients should help themselves by taking a positive attitude." We find that the great majority are very desirous of being able to do this and wish to be well. However, a "listening ear" is very helpful and encouraging.

To return to the dictum "Sublata Causa Tollitur Effectus." It should be apparent that the treatments which have been used with the best intentions have limitations. In the U.K. this condition, like polio, is usually due to enteroviral infection. However, there are many enteroviruses. To develop a vaccine for immunization would be ideal for prevention and would be much better than any "cure" but, the enteroviruses specific for the initiating illness would have to be defined before a vaccine could be prepared.

Nevertheless, prevention would be more effective than cure.

CHOLINE DIHYDROGEN CITRATE
SUMMARY OF FUNCTIONS

History

In 1932, Best and co-workers noted that dogs which had been depancreatised eventually developed very fatty livers, even though maintained on insulin. Varying dietary trials demonstrated that the substance responsible for alleviating this, was choline. However, it has other functions as we have shown over the years, the chief of which is its action as the precursor of acetylcholine which is the neurochemical which is active in intercellular neurological transmission.

Other functions which interact in protecting the human body include its role as a constituent of lecithin which is an important phospholipid. It also has been shown to prevent the deposition of fat in the liver and actually we have shown that it mobilizes lipids from arterial endothelium and other adventitious sites of deposition. It is also essential as a constituent of plasmalogens-these are essential for mitochondria, and also for sphingomyelin, which is important in brain tissue. The ascorbic acid in the formula sulphonizes the mobilized lipids and enables them to be water soluble and thus able to be renally excreted.

Choline is the precursor for acetylcholine and latter is synthesized from choline by acetyl transference and transported between brain and plasma via the capillaries. Thus the amount available to the brain depends on the

plasma concentration of choline.

Deficiency

Experimental changes observed include the deposition of fat in the liver and arterial walls. Certain renal lesions and also motor incoordination due to nerve degeneration have been observed. These are seen in humans. Vit. B 12 and also folic acid act as cofactors also with choline.

The work by Snorrason et al. from Reykjavik, on the trial of an acetylcholinesterase inhibitor in certain cases of M.E. showed an improvement. They postulated that a cholinergic defect-was central to the pathogenesis in M.E. They also showed that GHB resulted in improved sleep. However, in this work we consider that it is more in keeping with the natural chain to augment the acetylcholine itself, rather than inhibit the esterase.

Effects are not immediate dramatic effects. However, the effect of lipid mobilization is seen in the demonstrable rise in serum-cholesterol as a marker. Also, in a number of cases where there was an arcus, gradually resolved and in some totally disappeared. In the occasional case where there was a systolic murmur in the carotid(s) this has also resolved. Also, viruses are generally lipotrophic and the mobilization, sulphonation and renal elimination could be assumed to have a helpful effect in viral elimination.

TRIAL OF A SELECTIVE ACETYL CHOLINESTERASE INHIBITOR, ALANTHAMINE
HYDROBROMIDE, IN THE TREATMENT OF CHRONIC FATIGUE SYNDROME

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The purpose of the study was to search for means of diminishing the plight of patients with chronic fatigue syndrome (CFS) and to test the hypothesis that a colinergic defect is central to the pathogenesis of CFS. Forty-nine patients who fulfilled consensus criteria for CFS were treated with the acetylcholinesterase inhibitor, galanthamine hydrobromide.

Thirty-nine patients finished the study according to the protocol with 43% reporting 50% improvement, in fatigue, myalgia and sleep and 70% reporting

30% improvement whereas patients in the placebo group reported only 10% improvement in the same parameters of CFS. The improvement of patients on galanthamine was in most cases gradual and only reached significance for the group after four to eight weeks. The improvement was stable and no patients who reported over 50% improvement on galanthamine relapsed to a pretrial level of any symptom. One of the most surprising effects was the dramatic improvement of sleep disturbances that occurred in most patients in this medication: more than 60% of patients that finished the study reported over 70% improvement in sleep deficit. If this is indeed true it would be the first demonstration of a drug that can be used to correct sleep disturbance that influences a specific stage in normal sleep.

The most common adverse effect of galanthamine, as given in this study was mainly nausea that was dose dependent and reversible. Galanthamine hydrobromide is relatively safe and appears to be an effective medication against many symptoms of CFS. But the positive results of this study have to be interpreted cautiously because of methodological limitations of this trial. First, this study was originally organized as a double blind, placebo controlled trial, but was changed to an optional crossover after two weeks of treatment. Also the adverse effects of the active drug in 30% of patients would compromise the double blind.

With these limitations in mind it is all the same tempting to conclude that this study lends an indirect support to our hypothesis that a cholinergic deficit may play a role in the pathogenesis of the syndrome.