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Nicotinamide Adenine Dinucleotide (NADH) - a New Therapeutic Approach: Preliminary Results With Cancer Patients and Patients With Dementia of the Alzheimer Type

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ABSTRACT - The coenzyme nicotinamide adenine dinucleotide (NADH), also known as Coenzyme I, was used in oral form to treat cancer patients with metastases. In all the 12 cases so far under observation for more than a year an improvement in their clinical status has been observed. NADH has also been given to patients with dementia of the Alzheimer type. They were treated with 10 mg NADH tablets per day for 12 weeks. Significant improvement of the cognitive functions was observed.

Introduction

NADH is the abbreviation of nicotinamide-adenine-dinucleotide in its reduced form also known as Coenzyme 1. This coenzyme occurs in all living cells and plays a central role in the energy production of the cells (LEHNINGER, 1970). The more energy a cell needs, the more NADH it needs. For example, muscle cells and brain cells contain about 50 micrograms NADH per gram tissue, heart cells 90 micrograms, red blood cells 4 micrograms (KLINGENBACH, 1960). NADH was discovered in 1934 by Kaplan, an American scientist who found that it plays an essential role in the energy production of cells (KAPLAN, 1960). Since its discovery, it has been described in biochemical textbooks and has been used worldwide as a diagnostic tool in pure form in clinical laboratories (Biochemica Information Boehringer Mannheim, 1969). No therapeutic application was ever considered until 1988. On the basis of biochemical research, it was applied the very first time in 1988, at the Birkmayer Institute for Parkinson Therapy in Vienna to Parkinsonian patients in the form of intravenous infusions (BIRKMAYER, 1989

a, b, c). After three years of extensive research, an oral form of NADH was developed. These tablets have been given to more than two thousand Parkinsonian and depressed patients and showed a beneficial effect (BIRKMAYER et al., 1990 a,b, 1993) To date, after more than three years of clinical experience, no adverse reactions or side effects have been observed.

The reasons for using NADH in the treatment of cancer patients are various. First, NADH acts as an energy supplement providing the patient with more physical strength. This effect we have observed when using NADH to Parkinsonian patients. More than 2000 Parkinsonian patients have been treated so far with NADH and all of them reported a beneficial energetic effect related to this substance (BIRKMAYER et al., 1991, 1993).

The second reason was that NADH promotes phagocytosis by providing the necessary energy for the entire process (GRISHAM & EVERSE, 1982). Monocytes, macrophages and the polymorph nuclear leucocytes are capable of phagocytosis. All these cells are able to ingest foreign matters and most phagocytes are also able to extricate toxic material in order to kill foreign cells. This is a need for higher organisms to remove foreign matters such as bacteria or cell débris. Phagocytosis therefore plays a critical role in fighting and destroying cancer cells. During the first step of phagocytosis the metabolic activity in the phagocytic cells increases. Oxygen consumption rises considerably most of which is converted to superoxygen and hydrogen peroxide. This phenomenon is generally referred to as the „metabolic burst“ (ROOS and WEENING 1979). The production of large amounts of superoxyde and hydrogen peroxide appears to be one of the initial steps leading to the destruction of the ingested material. NADH plays an essential role in the „metabolic burst“ and so does NADPH. Assuming that additional NADH will provide further energy for the metabolic burst we started treating cancer patients with a stable oral, ingestable and absorbable form of NADH.

The reasons for treating Alzheimer patients with NADH were several. As has been shown by GOTTFRIES et al. (1984) that the deficiency of neurotransmitters in the brain of Alzheimer patients is not only restricted to acetylcholine but holds also for dopamine and noradrenaline. We have shown in in-vitro studies that NADH is able to stimulate the dopamine production in pheochromocytoma cells up to sixfold (VRECKO et al., 1993). Furthermore, it could be demonstrated that NADH applied intraperitoneally into rats increases the dopamine and noradrenaline biosynthesis in specific areas of the brain such as substantia nigra and nucleus accumbens (GARDIER, 1994, personal communications). Both brain regions play a central role in alertness and recognition. In addition, we found that symptoms of dementia which many Parkinsonian patients developed, in particular after longer duration of the disease, improved under the treatment of NADH (BIRKMAYER et al., 1993). All these observations prompted us to try NADH with patients suffering from dementia of the Alzheimer type.

Materials and Methods

Cancer patients criteria for selection

Patients included in our trial were selected on the basis that treatment with chemo- and/or radiotherapy became ineffective and that the disease was progressing. 6 patients have been included in the first trial and have been observed now for at least 9 months Alzheimer patients were selected on the basis of measurable cognitive dysfunction. They should exhibit a global deterioration scale of at least 3 and a mini-mental state score between 12 and 24. Other neurological psychiatric or clinical significant sytemic diseases, alcohol and drug abuse were exclusion criteria. The clinical assessment of the efficacy of the NADH treatment was performed on the basis of the global deterioration scale (GDS) (REISBERG et al., 1988) and the mini-mental state score (MMSE) (FOLSTEIN et al., 1975). The clinical assessment of the efficacy of the NADH treatment of cancer patients was done by instrumental tests such as X-ray, CT scan and MRI which could reveal changes in the size of metastases or of primary tumours.

Results

Cancer patient case descriptions

Case 1: Female, aged 63, August 1989, operation for invasive duct carcinoma. One year later multiple liver and bone metastases detected. Four therapy cycles, according to the CMF diagram, further increase of liver and bone metastases. Pain only reducible with the strongest analgesics. Since January 1991 NADH, initially three times a week 12.5 mg, intravenously, and then after four weeks parenteral therapy change to NADH orally, 5 mg every day. April 1991 radiological detection of metastasis regression, some foci greatly reduced in size and some completely disappeared. The oral NADH therapy was continued. A check in 1991 using CT scanning revealed a further marked regression of the liver metastases and the bone metastases were virtually undetectable. Patient free from pain and no longer requires analgesics. The serum concentration of CA15.3 dropped from 65.0 (Jan. 1991) to 24 (Aug. 1994).

Case 2: Male, aged 59, colon carcinoma three years earlier, 1990 sonographic and radiological detection of multiple liver metastases of cherry to plum size. Two chemotherapy cycles, Myleran or Endoxan unsuccessful, liver foci increased in size. December 1990 start of therapy with NADH, initially 12.5 mg intravenously three times a week and after four weeks change of therapy to NADH orally, 5 mg, every day. March 1991 sonographic detection of reduced liver foci size. June 1991 Check by CT scanning and sonography revealed an almost complete disappearance of the metastases in the liver. Subjectively the patient feels

extremely well. The tumor marker CEA was 110 (Dec. 1990) and declined to 22 by Nov. 1994.

Case 3: Female, aged 52, three years earlier quadrantectomy due to invasive scirrhous carcinoma of the breast. In January 1990 vertebral metastases were detected, April 1990 liver metastases were discovered by ultrasonics examinations. Therapy with Novaldex lead to no regression of the metastases. Also no response to a therapy cycle according to the CMF diagram was observed. November 1990 intravenous administration of NADH 12.5 mg every other day was stated. After four weeks it was changed to NADH orally, 5 mg every day. Two months after the start of NADH therapy clear regression of liver metastases, as well as disappearance/reduction of vertebral metastases. A Check in June 1991 revealed complete regression of the bone metastases. Liver metastases were greatly reduced or foci no longer detectable. CEA and CA15.3 were 45 and 92 by April 1990. The last control in October 1994 showed CEA to be 14 and CA15.3 to 18.5.

Case 4: Male, aged 66, February 1990 parvicellular bronchial carcinoma was diagnosed, multiple foci in both pulmonary lobes were formed. Cytostatic therapy with methotrexate and Endoxan led to no regression. In October 1990, NADH was administered parenterally (10 mg intravenously) every other day. Radiographic check in 1991 revealed the remission of the neoplastic foci both as regards to number and size. NADH therapy was continued with 10 mg orally every day. A Check in May 1991 by CT scanning confirmed a further reduction of tumor foci in both pulmonary lobes.

Case 5: Male, aged 72, November 1990 diagnosis of a tumor mass in the liver (8-10 cm in diameter). In summer 1993 multiple lung metastases of various size have been found in the CT scan. Patient denied surgical intervention as well as chemo- or radiotherapy. Since spring 1994 he is taking one tablet of NADH every day. Control examination by X-ray and computertomography showed no increase of the lung metastases and a reduction of the liver mass with indications of formation of necroses in the center of the tumor. The patient feels subjectively well and has no pain. The lung cancer associated tumor marker CYFRA 21-1 was 35 before NADH therapy (April 94) and 21 in December 1994. The carcinoembryonic antigen CEA levels were measured to be 67 in April 94 and 28 in December 94.

Case 6: Female, aged 55. February 1992 lymphnode metastases of an poorly differentiated mammary carcinoma were detected in left neck region. The CA15.3 value was 37.0, the CEA level 13.5 and the TPS 145 in March 1992. The primary tumor could not be localized. The patient denied chemo- and/or radiotherapy. She was given 5 mg NADH every day. A year later the previous palpable lymphnode metastase had disappeared. The tumor marker tests CA 15.3, CEA and TPS were 15.0, 8.0 and 95 respectively in July 94. Computer tomography and bone scan did not show any metastases (June 94).

Patients with dementia of the Alzheimer type

Case report:

Case 1: A 79-year old female patient living in New York had been diagnosed dementia of the Alzheimer type at Mount Sinai Hospital. She was unable to tell the time and the place where she lives and to name objects. Her mini-mental state rating was 6 before therapy. Her global deterioration scale (GDS) was 6. Indicating severe cognitive decline, she was entirely dependent on care-givers and was largely unaware of recent events and experience in their lives. The patient received 2 tablets of NADH (5 mg per tablet), total daily dosis 10 mg every day. After 2 months, the patient was examined again and revealed a remarkable improvement of her cognitive function and mental capabilities. She was able to name objects auch as a car, aeroplane, streets, bridges. Objectively, her MMS scale increased to 18 and the GDS value decreased to 3. The patient is taking NADH on a daily basis now for more than 9 months without any adverse or side effects. The care-giver realized additional slight, but significant improvements.

Case 2: A 61-year female patient living in Italy was the manager of a medium large company before. Symptoms of cognitive disfunction were revealed. She had been diagnosed dementia of the Alzheimer type at the University of Rome before she visited our institute in Vienna. At our examination she was unable to name simple objects such as table, chair, window or a door. She could not complete sentences. However, she realised her incapability to communicate with people at her home or per telephone and therefore her impetus for conversation was rather low. Her mini-mental state score was 12 and the GDS rating scale was 6 before starting the therapy. She received 2 tablets NADH every day (10 mg total daily dosis). After 2 months of therapy the patient was reexamined again. A remarkable improvement could be observed. The mini-mental scale rating increased to 21 and the GDS rating to 4. The patient has been taking 10 mg NADH for more than 6 months now. No side-effects were reported from the care-giver nor did the patients complain of any.

Case 3: A 63-year old male patient had noticed symptoms of forgetfulness and problems with recognition for about 6 years. A neurological examination revealed clearly diminished mental capacity with a MS value of 10 and a GDS value of 5. The patient was diagnosed with dementia of the Alzheimer type. After treatment with 10 mg of NADH orally daily, he was examined again after 10 weeks. The cognitive abilities clearly had improved. He could solve simple mathematical problems such as additions and had no difficulty in finding words. His MMS value rose to 22, his GDS value was determined to be 3. This patient was the very first to be treated with NADH. After 4 months the treatment was discontinued for 1 year. During that period a decline in certain brain functions was observed. The MMS value decreased to 16 and the GDS score to 4. On the patient´s wish a renewed oral treatment (10 mg NADH per day) was started which led to an improvement of the brain function after 2 months which was even slightly better than before stopping the therapy.

Case 4: A 69-year old female patient had been forgetful for a few years and stated that her condition had deteriorated. She could not longer find her way back home after going shopping no longer knowing what she was supposed to buy. She could not find her way about in her own house and could not find her way from one room to the next. Her mini-mental state was a score of 8 and her global deterioration score (GDS) was 5. The patient was diagnosed in the department of neurology as dementia of the Alzheimer type. The patient then received 10 mg of NADH daily and was reexamined after 2 months of treatment. A significant improvement of the cognitive abilities had been noticed. The patient was able to go shopping, find her way around her home and could watch television and retain almost all what she had seen. Her mini-mental state score increased to 20 and her GDS value decreased to 3. The patient has been under treatment now for more than 6 months and the condition improved again gradually. No side-effects were observed nor did the patient complain of any.

Case 5: A 55-year old female patient exhibited a serious limited mental capacity. The patient´s vocabulary was extremely deficient, she frequently repeated words and exhibited a fixation on certain reiterations. She had great difficulties in reading simple sentences and she failed to understand their meanings. The patient could not perform the simplest of arithmetics and she was unable to contact. Her mini-mental score was 8 and her GDS value was 6. From this number it was deduced that the patient was suffering from dementia of the Alzheimer type. The patient received 2 tablets of NADH (5 mg per tablet) daily for 2 months before she visited us for a reexamination. After 2 months of therapy her cognitive function had distinctly improved, her short time and long time memory had increased and she could perform simple arithmetics and explain the meaning of proverbs. The GDS value had sunk to 3 and her MMS score had increased to 22. The therapy with NADH was continued on a daily basis of 10 mg orally. No side effects were observed during this extended therapy. Slight, but consistant improvement had been reported by the care-giver.

Case 6: A 65-year old male patient exhibiting significant forgetfulness and apathy. A neurological examination revealed a strong limited cognitive capability and impaired temporal and spacial orientation ability. The patient could not state the current date nor recall any recent news. His MMS was 10 and his GDS was 5. Neurologically he had no organic pecularities. The patient was diagnosed dementia of the Alzheimer type. 10 mg of NADH in form of 2 tablets of 5 mg were administered daily for a period of 8 weeks. After the therapy the patient exhibited a distinct improvement in his recollection capacity. He could state the correct date and he could recall news which he had heard. His MMS score rose from 10 to 21, his GDS values decreased from 5 to 3.

Case 7: A 57-year old female patient exhibited a serious limited mental capacity. She was unable to recognize and name objects and could not repeat words or short sentences. Simple arithmetics (single digit multiplication) as well as reading were not possible and she had no sense of time or place. She exhibited no neurological or organic peculiarities. Her mini-mental state value was 4, her GDS score was 6. The patient was diagnosed as having the dementia of the Alzheimer

type. 10 mg NADH were given orally on a daily basis for 10 weeks. After that period an examination was conducted and revealed that the patient´s cognitive abilities had significantly improved. The patient could perform simple arithmetics and draw simple conclusions by deductive reasoning. Her spacial and temporal orientation abilities were significantly improved. Her MMS score had risen to 16, her GDS value had dropped to 4. Thereafter, the same 8 week long therapy was repeated for another 2 months. The improvement of the patient´s condition was maintained during the extended therapy and no side-effects were observed. The patient stated that she felt much better physical as well as mental when taking NADH.

Discussion

Cancer patients

The observation we made with our cancer patients when treated with NADH was twofold: First, the patient himself felt physically and psychically considerable better than before the NADH therapy. Second, there was a regression of the disease reflected by decrease in the size of the metastasis or the primary tumour which has been verified by CT scan or magnetic resonance. The mechanism how NADH acts in these cancer patients is unclear. For the time being one can only speculate on the molecular processes which are triggered and promoted by NADH. One assumption is that NADH provides additional energy to the cancer cells which may induce a differentiation process. NADH, also called Coenzyme I, is the key element in the energy production of a cell which takes place in the mitochondria. As shown in tissue cultures, NADH passes the cell membrane and goes into the mitochondria (VRECKO, unpublished observation). It also increases the activity of the enzyme NADH ubiquinone reductase which is regarded as the Complex I in the respiratory chain located in the inner side of the mitochondrial membrane. Whether this additonal energy will cause a better regulation in the direction of differentiation of the cancer cell remains to be elucidated. Another possibility could be that NADH increases the phagocytolytic capacity of leucocytes during the „metabolic burst“ a process which is triggered when leucocytes come in touch with foreign matters or cell débris (ROOS & WEENING, 1979; GRISHAM & EVERSE, 1982). These cells need the energy to ingest the foreign material and to destroy it against cancer cells. This energy is mostly derived from glycolysis (SBARRA and KARNOVSKY, 1959). Whether NADH stimulates the cellular immune response has not yet been investigated. Some indirect evidence can be derived from preliminary findings in which NADH stimulates the neopterin biosynthesis in neuroblastoma cells (VRECKO, personal communication). Another possibility which has to be looked at is the influence of the neurotransmitter dopamine on tumor growth. There are epidemological studies indicating that Parkinsonian patients when treated for a longer period of time with L-Dopa, a precursor of dopamine, have lower incidence of cancer or if one develops it shows a much slower growth rate. This could be due to an

overflow of the organism with dopamine which may have an inhibiting effect on the proliferation activity of cancer cells. We have shown in over 800 Parkinsonian patients that NADH increases the dopamine level in the plasma and the dopamine metabolites in the urine. Furthermore it has been shown in the pheochromocytoma cells that NADH is able to stimulate dopamine production sixfold (VRECKO et al., 1992). Further studies are on the way to show whether cancer patients who are on NADH treatment have higher levels of dopamine in their plasma than cancer patients without NADH.

Although the number of patients we have treated so far with NADH is rather low, the observations made are remarkable. Taking into account that numerous cancer patients do not respond to the classical therapy of chemo- and radiotherapy, NADH may represent a potential alternative in particular as it is a safe naturally occuring substance. The 10 mg NADH we have applied corresponds to approximately 0.014 mg/kg body weight. The maximum tolerated dose of NADH given to dogs intravenously for 14 days was found to be 500 mg/kg. This is more than 7000 times more than the dosage which we have applied to our patients.

Alzheimer patients

Our clinical trial using NADH as new therapeutic approach for demented patients was based on the findings of GOTTFRIES et al. (1984) that the brains of these patients not only have a deficit in acetylcholine but also in dopamine and noradrenaline. From our studies with Parkinsonian patients (BIRKMAYER et al., 1989a,b) we learned that NADH increases dopamine biosynthesis and with it the features related to dopamine activity such as posture, strength, mobility and libido. As dopamine is a direct precursor for noradrenaline an increase in dopamine caused an elevation of the noradrenaline content in those particular brain areas. The increase in noradrenaline concentration is reflected by a higher alertness, spontaneous reactivity and emotional participation. In a number of our patients we found that the dopamine and the noradrenaline metabolites in the urine were also elevated after NADH therapy. Whether or not this increase in dopamine and noradrenaline is responsible for the improvement in cognitive functions is presently elucidated.

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