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Anorexia nervosa and sudden death in childhood: clinical data and results obtained from quantitative neurohistological investigations of cortical neurons

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Abstract A crude rate of mortality of 5.9% has been quoted for Anorexia nervosa (AN) in recent studies. There are different causes of death ranging from suicide to sudden death. Autopsy data are extremely rare about brain alterations in deceased AN patients. Reported in this study is a female patient, aged 13.5 years, who died of acute AN. Quantitative neurohistological investigation post mortem was performed on her brain. Results were compared with data obtained from a girl of the same age with no contributory neuropsychiatric findings. In the cortex of the anorexia case beside typical pyramidal neurons, a slim neuron type with one extremely long basal dendritic field was found to occur more frequently than normal. In the neurons of the AN case, the ramification pattern of single basal dendritic fields was found to be reduced and changes in the spine morphology, as well as reduction in spine density, were observed. However, a simultaneous lenthening of the terminal dendrites of higher order gave some evidence for repair mechanisms and neuronal plasticity. The AN-specific implications of these findings are discussed. The conclusion is that all AN deaths should be reported together with descriptions of causes and cerebral alterations.

Key words Anorexia nervosa · Childhood · Sudden death · Cortical neurons

Introduction

In almost all studies of anorexia nervosa (AN) only general reports have thus far been presented on causes of death in individuals who die from this disease. Steinhausen et al. (1991), in four decades of follow-up studies on AN, provided percentual data on mortality rates together with the following classification of causes of death: death due to AN, death due to anorexia-related medical conditions, death due to other illness, death due to suicide, death due to accident and death due to other, unspecified causes. Highly diverse data on the crude mortality rate of AN have been reported from a 20-year follow-up study by Crisp et al. (1992) who derived 4% (St George's cohort) and 13% (Aberdeen cohort), and from a meta-analysis of 42 published studies on AN by Sullivan (1995) who derived 5.9%. Therefore, the suggestion by Hsu (1992) appears to be justified when he proposed that all deaths should be reported together with descriptions of the causes. The severity of the disease is determined, last but not least, by a great variety of reversible physical alterations (Palla and Litt 1988; Patchell et al. 1994; Sharp and Freeman 1993). However, the underlying causes of conspicuous cerebral manifestations of AN have not been elucidated as yet, such as atrophy and pseudo-atrophy of the brain or neurophysiological and neurochemical alterations.

An attempt is made in this paper to find answers to some of the questions involved by the example of a female patient who died of acute AN at the age of 13.5 years and whose brain was subjected to a quantitative neurohistological investigation (right hemisphere, precentral gyrus, Brodmann's areas 4 and 6).

Case description

The patient, aged 13.5 years, on admission to hospital, was 28.2 kg in body weight, 155 cm in body height and 11.75 in body mass index (BMI), after she had started to reduce eating 6 months before hospitalization. Blood pressure of 95/60, pulse rate of 60/min, scaly-dry skin, constipation and a few peristaltic sounds were additional findings on admission. There was no vomiting, and the question for abuse of laxatives was negatively answered.

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The patient complained about a feeling of fullness. No contributory findings were recorded from thorax X-ray, computed tomography (CT), sonography, abdominal checks and multiple electrocardiogram leads. All laboratory values were close to lower limits. Neurological examinations did not provide relevant clues. The patient's psychopathological profile was characterized by bashfulness, diffidence, overadaptation and reduced impulse. She described social and separation-related anxieties and exhibited changes of mood between sadness and dysphoric irritability. Manifest impairment of body identity was accompanied by massive rejection of food uptake.

The patient was the second child of parents who were both in good health. Her mother had always been very slim and rated herself as a "poor eater". Her brother, aged 16 years, attended the tenth grade of a secondary school. At the age of 13 years, he had been hospitalized for "akathisia", followed by tiapride medication on an outpatient basis. The patient was born 3 days over term after normal pregnancy. Her birth weight was 3500 g and her body length 49 cm. Early childhood was without any conspicuous events, apart from poor eating and drinking up to the age of 1 year and timid behaviour in infancy. Her performance at school was excellent and driven by ambition. The patient still was in premenarche at the time of admission to our hospital.

On the first day of treatment, the patient accepted some food for all six meals offered, but she complained about abdominal pain. On the second day, moderate eating was followed by repeated vomiting and continued complaints about abdominal pain. The therapy was continued, using infusions. Further diagnostic investigation of the abdominal region did not reveal abnormal signs, except for stomach dilatation. Vomiting recurred on the evening of the fourth day of treatment and later was followed by acute cardiovascular collapse. Cardiac action was restored by 40 min of heart massage. The patient was kept under artificial respiration. Her blood pressure was 50/24 mm Hg and her heart rate 60/min, her comatose condition being unchanged and, subsequently, worsened by development of a second-degree bulbar brain syndrome. Bedside-recorded electroencephalograms 2 hours before death showed a predominance of an isoelectric curve.

Autopsy findings

The autopsy findings (5 h after death) were (a) trachea and lung: hyperaemia; (b) heart, kidneys, pancreas, thyroid: interstitial fibrosis; and (c) hypophysis: focal fibrosis.

Neuropathological findings

The following *macroscopic* findings were obtained: brain weight (fixed) 1535 g, and flattened cerebral convolutions pointing to brain oedema; first-degree pressure cone of cerebellar tonsils, right more than left; stenosis of lateral ventricles; brain anaemia.

The following *microscopic* findings were obtained: macrosections (cerebellum with medulla oblongata, thalamus and mesencephalon) with no large pathological lesions; narrowing of fourth ventricle; in the cerebrum, pericellular intracortical oedema, venostasis and oedema of the leptomeninx; severe laminar oedema in the temporal lobe; in the basal ganglia, perivascular oedema; in the pons and medulla oblongata, perivascular and pericellular oedemas, defects of Purkinje cells; rarefaction of the granular cell layer; in the dura mater, circumscribed micronodular proliferation of meningothelia.

Quantitative morphometric findings (Golgi method)

Formalin-fixed tissue pieces of the precentral gyrus (Brodmann's areas 4 and 6) from the right hemisphere of the AN case as well as from a control case were placed in impregnation solutions for Golgi modifications, Golgi-Kopsch or Braitenberg. Coronal tissue slices, 200 μm in thickness, were cut from throughout the cortex. As control we used an autopsy case of a girl without neuropsychiatric anamnesis (aged 11 years, 10 months) who died suddenly after complications of abdominal surgery. In both cases properly impregnated pyramidal neurons located in layer V were classified into two different types (Fig. 1). Type-I neurons, in both cases the most frequent cell type, are regular pyramids which develop one mighty apical main dendrite, surface oriented, with lateral and terminal ramifications and, basally, a corona of stem dendrites which ramify densely and extend more or less symmetrically in horizontal or inclined-downward direction across the neuropil around the soma (Fig. 1 a, b).

Type-II neuron (very rarely occurring in the control case) is a slim type of pyramidal neurons. These cells are characterized by one extremely long basal dendritic field of vertical orientation and deep extension in or through the sixth layer, almost up to the subcortical white matter. It should be noted that both types occurred in the AN as well as in the control case; however, this slim neuron type was found in the Golgi specimens from the AN case more frequently and seemed to be less spiny exept for the long deep dendrite (Fig. 1 c, d). Type-II neurons make up approximately 25% of all cells measured in the AN case.

A three-dimensional computer-assisted method was used for the measurement of the neurons (Uylings et al. 1989) classified in preparations from the AN case and the control case. Measurements were performed in the pericaryon (soma size, number of basal dendritic trunks) and in single dendritic fields (SDF) of the basal dendritic tree: The SDF is a part of the dendritic tree and consists of all ramifications arising from one basal dendritic trunk. Only completely impregnated SDFs were measured. The parameters estimated in an SDF are found to be characteristic for the dendritic development or degree of ramification/differentiation of a given neuron and can be used as a statistically independent entity (Schönheit and Schulz 1982). All parameters measured are listed in Table 1 and results are presented in Fig. 1. Due to the ramification, the den-

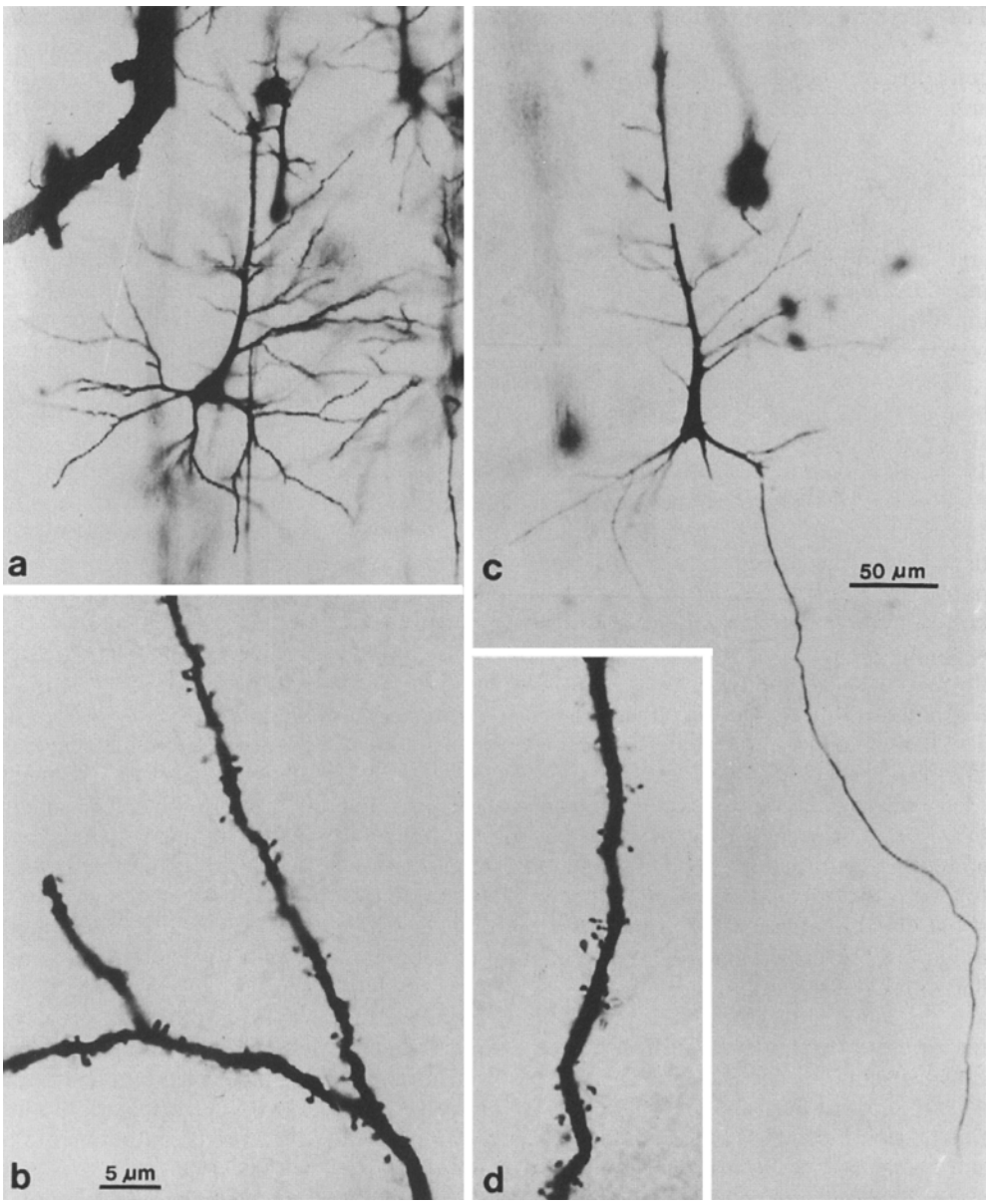

Fig. 1 a–d Photomicrograph of cortical lamina-V-pyramidal neurons type I **(a)** and type II **(c)** with their dendrites in higher magnification **(b, d)**. To demonstrate the typical feature used for classification of the neurons in both cases, the example of **a, b** type-I neuron was taken from the control case, and the example of **c, d** type-II neuron was taken from the anorexia nervosa case where it occurred more frequently. The dendrites show visible examples for the spine morphology and arrangement. (Magnification **a, c**: *bar* = 50 µm; **b, d**: *bar* = 5 µm)

dritic tree of an SDF is divided into segments (orders). The length of a segment is the parameter of the distance between two ramification points. The last segment up to the tip was called the terminal segment. The maximum radial extension of the SDF is the distance from the middle of the pericaryon up to the most distant tip of a terminal segment, a parameter for the spatial distribution area of the neuron. Length measurements were registered in three dimensions automatically by following the dendrites in 1000-fold magnification (oil immersion) and all visible spines were counted. The spine density is the quotient of spine number and length of the SDF. Summarizing or statistical calculations were undertaken using the Statistical Package for Social Sciences (SPSS) program. Altogether, measurements were made of 80 neurons or 180 SDFs. Mean values were compared by the parameter-free U-test of Mann and Whitney based on the SDF as statistical entity (significance level 5%).

Reduced soma size and fewer basal dendritic trunks were found in type-I neurons. Both cell types exhibited reduced lengths and reduced spine density at the single basal dendritic field. The distance between ramification points (average length of dendritic segments) was also reduced.

Significant differences in the number of ramification points, dendritic segments or free terminals were obtained only in type-I neurons because the type II was highly variable and less frequent. The maximum radial extension (largest in type-II neurons of the control case) was also restricted in the AN case (Table 1). In order to find out whether this reduction in length and spine density was specific to defined parts of the basal dendritic tree (intermediate or terminal segments), a data analysis along the dendritic orders was performed (Schönheit et al. 1996). It was found that intermediate segments were less affected. The length reduction was found mainly in the terminal

Table 1 Quantitative morphometric data (mean ± SD) of the measurements on type-I or type-II lamina-V-pyramidal neurons in anorexia nervosa and the control case

Parameters of pyramidal pericaryon and basal dendritic field	Anorexia nervosa		Control	
	Neuron type I	Neuron type II	Neuron type I	Neuron type II
Area of soma (μm^2)	201.74[a] ± 147.89	267.13 ± 142.31	321.09[a] ± 157.27	230.80 ± 169.77
No. of basal dendritic trunks	5.82[a] ± 1.26	6.00[a] ± 1.50	7.65[a] ± 1.08	8.80[a] ± 1.79
Total length of dendrites (μm)	588.38[a] ± 317.16	853.98[a] ± 663.12	1192.75[a] ± 474.60	1499.06[a] ± 920.52
Total no. of spines	119.24[a] ± 95.82	140.30[a] ± 130.71	331.63[a] ± 169.36	335.50[a] ± 297.54
Spine density (spines/μm)	0.19[a] ± 0.08	0.15[a] + 0.08	0.27[a] ± 0.07	0.24[a] ± 0.09
No. of segments per dendritic field	8.36[a] ± 3.99	9.47 ± 5.31	11.10[a] ± 6.42	11.33 ± 7.11
Ramification points	3.61[a] ± 1.94	4.17 ± 2.62	5.02[a] ± 3.21	5.08 ± 342
No. of free dendritic terminals	4.75[a] ± 2.06	5.30 ± 2.70	6.08[a] ± 3.21	6.25 ± 3.70
Average length of dendritic segments (μm)	182.19[a] ± 79.20	195.95[a] ± 70.37	302.28[a] ± 154.90	391.04[a] ± 378.79
Maximum radial extension of SDF (μm)	202.10[a] ± 78.86	375.12 ± 272.02	300.67[a] ± 77.59	454.15 ± 316.45

[a] Significant differences ($P < 0.05$)

segments of lower order in both neuron types. However, type-II neurons developed tendencies to elongated dendritic terminals arising after five to eight ramifications (higher order), sometimes with increased spine density.

In type-II neurons of the AN case many spines at long terminal segments were classified as the super-long type of thin spine, known as a less mature stage in spine development (Fig. 1 d). This type was observed by Purpura (1975) in human fetal cortex or in cortex of patients with mental retardation. In animal experiments, the same spine type was identified in undernourished rats (Schönheit and Haensel 1984). It should be emphasized that these changes were found only occasionally, but were always of distinct nature.

Discussion

The complex aetiological questions of AN have not been satisfactorily answered. The most recent insights in this context have been expounded by Braun and Chouinard (1992). Findings with regard to neurotransmitters, neuropsychology and neurophysiology seem to suggest that AN might be attributable, among other things, to a genetically determined and/or acquired dysfunction of the right hemisphere. Therefore, the question arises for the cause and consequence of severe malnutrition, weight loss, cachexia on the brain as such as well as on the morphology of the cortical neurons. In many clinical reports a diffuse generalized pseudoatrophy of the brain cortex was demonstrated in CT or magnetic resonance imaging (MRI) investigations. Enlargements of the inner or outer liquor spaces point to atrophic processes in the cortical neuropil as well as in the white matter. In previous experiments on the influence of chronic undernutrition during the maturation of the brain, we found in pyramidal neurons of the limbic cortex of rats significant reduction in the dendritic arborization and spine density. High plasticity of these neurons and some degree of reversibility of the length reduction of the dendrites under conditions of rehabilitation and successful therapy were seen (Schönheit 1982).

In the case reported herein, the quantitative neurohistological results are in good agreement with the frequently reported pseudoatrophy and/or acquired dysfunction of the right hemisphere in clinical AN cases (Braun and Chouinard 1992). The question arises about reversibility or irreversibility of the pseudoatrophy and correlation with impairment of cognitive or motor functions. The findings thus far obtained differ from each other. Fox (1982), for example, provided evidence to specific impairment, whereas Laessle et al. (1989) did not find any relationship between CT-proven atrophy, severity of symptoms and duration of illness, on the one hand, and cognitive performance, on the other. However, all examiners described variably pronounced cortical and subcortical atrophy recordable from AN patients by means of CT and MRI. Yet, different answers are given to questions for the causes of pseudoatrophy or atrophy and reversibility or irreversibility and for the reason why similar alterations have been recordable also in bulimia patients with normal body weight (Hoffman et al. 1989; Husain et al. 1992). Both CT and MRI examinations of AN patients in childhood and adolescence are rare (Kornreich et al. 1991). None of the techniques used – CT, MRI, positron emission tomography (PET), single positron emission tomography (SPECT) and nuclear magnetic resonance (NMR) spectroscopy – have thus far made a positive contribution to causative elucidation of the brain-volume variations or alterations to inner and outer liquor spaces in AN cases. In addition to frequently discussed dehydration and rehydration effects, vitamin and electrolyte deficits and protein changes, considerations and discussions have to include also aetiological factors of different nature at neuronal and glial levels. Partial or incomplete regression of atrophy was reported by Nussbaum et al. (1980) following CT analysis of 14 AN patients in childhood and adolescence. An average age of 14.1 years was recorded from the group with CT normalization (loss of body weight by 22.1%, length of illness 14.1 months), whereas an average

age of 15.7 years was established for the group with persistence of abnormal CT findings (loss of body weight by 35.2%, length of illness 10.6 months). The existence of a correlation between weight loss and duration of illness appeared to be the most important contrast between the two groups. Patients with abnormal scans lost more weight over a shorter period of time than those with normal scans. Similar findings were obtained by Artmann et al. (1990) from CT examinations of 31 adolescents and four adult patients (average age 26 years), the data of the adolescents being 11.5–17.8 years of age, 14 years of average age, duration of illness 2–14 months, and weight loss 12.5–58 or 26.4% on average. Lowering of plasma protein was considered by the authors a possible aetiological cause of reversible enlargement of the cerebrospinal fluid space.

In our neurohistological investigation we concentrated our interest on the right hemispheric motor area and the comparison of the neuronal structure of dendritic arborization between the AN and the control case. The interpretation of our results is of course preliminary and limited by the lack of measurements in other areas of the right hemisphere, in the contralateral cortex, in some relevant limbic areas (hippocampus, amygdala or cingulate) or to consider the hypothalamohypophyseal system. The method of Golgi impregnation is difficult, and a sufficiently large number of well-impregnated neurons in each case is necessary for the quantification. Therefore, the open question cannot be answered satisfactorily if in AN patients the regressive neuronal changes reflect an imbalance in the hemispheric development, eventually in favour of the left side and relative dystrophy of the right side.

However, our own neurohistological findings, necessarily, should be interpreted in connection with the age of the patient described in this paper, length of illness, course of disease, conditions which led to sudden death and the time which elapsed from death to brain autopsy (5 h). The case history seems to support the assumption that the onset of the disease was not less than 6 months before acute hospitalization, i.e. in the patient's twelfth year of age. Her body weight of 28.2 kg, BMI of 11.75, actual loss of weight by 25.8% against standard loss by 43% and her eating behaviour seem to support the assumption of an AN of the restrictor type (type I). As far as changes of laboratory values are concerned, our patient was similar to cases reported in the literature, in that many of her parameters were below normal, such as protein, potassium, blood values and albumin, its critical predictor value being $\leq$ 36 g/l. Protein and potassium deficits may have played a particular causative role for sudden death, although no contributory findings were recordable from ECG in general and the Q–T interval in particular.

Hanefeld et al. (1993) used NMR spectroscopy to examine AN children and detected significant drop in choline in white matter. Choline is a module for myelin and is responsible for fatty acid transport. Occurrence in AN patients of deficiency of selected essential fatty acids associated with compensatory changes in non-essential fatty acids and decreased fluidity of plasma lipids has been recently reported by Holman et al. (1995). Holman et al. (1989) had previously described the similarity of poly-unsaturated fatty acid (PUFA) profiles of multiple sclerosis with those in four other virus-associated syndromes. The authors added that the similarity of PUFA profiles of phospholipids in AN with comparable profiles in multiple sclerosis was just as striking phenomena and that a survey of AN patients for evidence of viral infection might provide a revelation. The authors felt that their observed fundamental changes in membrane structure might well be closer to the root cause of AN than the inanition and psychological aberrations associated with the disease. These findings and constellations would move AN closer to a post-viral-onset disease, as was recently discussed in the context of four cases by Park et al. (1995). The very fact of choline deficit, after all, is of particular interest also with regard to the neurotransmitter acetylcholine.

Choline deficit may reduce the availability of the neurotransmitter acetylcholine which is released by the afferent cholinergic terminals at cortical neurons. Evidence was provided to such alterations by changes at postsynaptic level which occurred also in our measurements. We found in regular neurons (type I) significant reduction in ramification, length and spine density over the entire basal dendritic field. Terminal dendrites were mainly affected. Intermediate dendrites showed spine losses only. The spine-type pattern was changed with occurrence of the long thin type pointing to quantitative and qualitative impairment of interneuronal contacts in the AN case. The terminal segments of the dendritic tree obviously may reflect progressive or regressive changes. Shortening of terminal dendrites in lower orders, as observed in the AN case, was indicative of certain stagnation of growth. However, lengthening of terminal dendrites in higher orders in type-II neurons, on the other hand, seemed to be indicative of repair mechanisms of remedial action on length and spine losses in intermediate segments. The potential for elongation of terminal dendritic segments may be present in neurons throughout life (Huttenlocher 1974; Coleman and Flood 1986; Schönheit and Kuchinke 1994). This aspect of functional compensation in type-II neurons in the AN case was reflected also in trends towards higher spine densities in these elongated terminal segments. The impairment in the spine distribution pattern goes along with changes in spine morphology: The main types of thin, long, mushroom-like or stubby spines were detectable from control and AN samples, however, with predominance of the thin form in AN. This may be associated with the dendritic repair trends. Elongation of the spine neck may be conducive to the formation of new axospinodendritic contacts. In animal experiments after starvation-induced spine reduction, thin elongated spines were recorded more frequently in adult animals, although this should be normal only in previous stages of development (Schönheit and Haensel 1984). Spine morphology may reflect the functional efficacy of synaptic transmission, as has become known from potentiation experiments (Chang and Greenough 1984; Perkel and Perkel 1985; Spacek 1985). Shortening of spines may be caused by stimulating effects of the environment (Berbel et al. 1985; Schüz 1986). Very

long spines were observed in the fetal period and, subsequently, in mentally retarded patients by Marin-Padilla (1974) and Purpura (1975, 1983).

In this context the question arises if the morphology or neuronal cells with Golgi impregnation of human postmortem brain tissue is affected by the circumstances ante finem and the time elapsed between exitus and autopsy. In the interpretation of the data obtained from our patient with AN, this time was short. Likewise, we consider the time in coma before death much too short to initiate ramification changes. The pericellular oedema was localized mainly in the superficial cortical layers I and II, and our investigation concentrated on the deepest layers V and VI. Therefore, we see our results in close relation to AN. However, in the literature there are some hints that after long-term premortal metabolic encephalopathia the Golgi method may show limitations (Williams et al. 1978).

The phase of neuronal network maturation may be adversely affected by phases of starvation, with protein and/or energy deficits causing cascades of metabolic abnormalities which are responsible for neuronal changes in the degree of ramification as well as for disturbance of synaptic contacts. As a multiplier of the severity of neuronal alterations, acquired minimal brain dysfunction, possibly of perinatal origin, should be considered. Minimal early acquired brain damage was revealed in a CT study for 60% of the anorectic patients (Artmann et al. 1985), as a predisposing factor for clinically manifest AN. In humans, acquisition of higher cognitive skills and capabilities during advanced childhood and early adolescence is accompanied by structural reorganization in the neuronal network. Included in such reorganization are not only processes which destroy functionally insufficient overshoot growth of dendrites and synapses during childhood, but also processes which improve stabilization of functionally effective synaptic contacts and give rise to evolution of the adult pattern (Poljakow 1979) of neuronal interaction along with independent strategic thinking and skill. The coincidence of regressive and repair mechanisms together with the known high plasticity of neurons at the age level of our patient should open possibilities for reversibility of the majority of neuronal changes at the dendritic level in AN.

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