Iron Deficiency Syndrome (IDS)

A multicentre descriptive study of drug monitoring

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Introduction

In particular, women who menstruate often suffer from symptoms such as fatigue, depressed moods, sleeping disturbances, headaches etc., which we first described in 2006 as Iron Deficiency Syndrome (IDS) (1). Often the initial symptoms already occur, as described in the above-mentioned publication, in the case of ferritin values below 50 ng/ml.
In this study, it was investigated what impact quick individual loading doses of iron infusions - with a target ferritin value of 200 ng/ml - have on the existing symptoms of patients with a ferritin value < 75 ng/ml in the case of low ferritin values, if this therapy is performed in accordance with a recently developed concept. In addition to the questions examined in 2006, for this study the symptoms in correlation with age and ferritin groups, as well as the problem of anemia, were investigated.

Methodology

Data was gathered from 20 iron clinics (19 in Switzerland and 1 in Berlin). The therapy processes were documented in an Internet databank within the framework of a prospective descriptive drug monitoring study which took place between March 2006 and November 2007. From the cohort of patients examined, mainly women who menstruate and children reported experiencing fatigue, difficulty when concentrating, depressed moods, sleeping disturbances and headaches.

In order to establish the indication for IDS, the complaints were compiled on the basis of a questionnaire and the relevant laboratory values (CRP, Hb, ferritin, LTR, TF) were determined. If an iron deficiency was present at the same time as the above-mentioned symptoms and it was possible to eliminate other potential causes, as well as contraindications, an iron infusion treatment was performed immediately. The amount of iron that was necessary for an optimal loading dose in each individual case was calculated using a computer program in the health-banking system[1].The patients subsequently received 200 mg of iron twice weekly via an infusion over an individually calculated period of time.

All treatments were administered using short infusions with iron sucrose (Venofer). Iron carboxymaltose (Ferinject) was, initially, not used. The new drug appears not yet to have been sufficiently researched for clinical use (e.g. Non-approval letter from the FDA dated 12.3.08).

After the loading dose, as well as 3 months afterwards, a follow-up check on the patient was carried out. The symptoms and laboratory values were once again recorded. On the basis of the ferritin values identified after 3 months and taking into consideration the current symptoms, the continued therapy was subsequently determined. Also with regard to an effective relapse prevention, the individually required amount of iron can be calculated using the computer program in the health-banking system.

[1] Health databank on the Internet for quality management

In order to document the therapy success, the symptoms and the laboratory data were recorded before and after the loading dose, as well as three months afterwards, and were entered into an Internet databank. The data after the loading dose via an iron infusion was compared to that before the beginning of therapy.

Results

In total, 873 patients satisfied the inclusion criteria and they were included in this prospective drug monitoring study and/or treated with iron infusions. The relevant data before and after the loading dose was documented for all 873 patients. In the case of 583 patients a follow-up check was carried out after another 3 months.

92% of the cohort of patients were women and 8% men and the two groups were on average 39- and 31-years old respectively. 27 patients (3%) were younger than 15-years old (12 girls and 15 boys with an average age of 12 and 11 years respectively). As is evident from **Table 1**, the most frequently reported symptoms before the loading dose were fatigue (84%), difficulty concentrating (57%), followed by depressed moods, neck tension and headaches each with 49%, as well as dizziness (45%) and sleeping disturbances (42%).

Difficulty concentrating and fatigue with 63% are the most frequently mentioned complaints among children, followed by sleeping disturbances (33%) and headaches (30%) - symptoms which characterize an ADD.

Table 1: Frequency of symptoms (in %) correlated with age groups

Symptoms (n = 873 patients)	Frequency in patients with iron deficiency	< 15	15-20	21-30	31-40	41-50
	n = 873	n = 27	n = 103	n = 176	n = 240	n = 327
Fatigue	84 % (n = 732)	63 %	77 %	88 %	88 %	87 %
Difficulty concentrating	57 % (n = 495)	63 %	57 %	57 %	58 %	59 %
Depressed moods	49 % (n = 425)	6 %	34 %	48 %	54 %	54 %
Neck tension	49 % (n = 430)	6 %	27 %	50 %	52 %	55 %
Headaches	49 % (n = 429)	30 %	38 %	53 %	50 %	51 %
Dizziness	45 % (n = 390)	12 %	34 %	49 %	46 %	43 %
Sleeping disturbances	42 % (n = 364)	33 %	37 %	40 %	39 %	47 %

What is striking is that the number of symptoms existing at the same time increases up to the age of thirty and remains hereafter quite constant. (**Diagram 1**). Children under 15 have on average 1.7 of the symptoms, the 15-20-year olds 3.6 and the over-twenties between 4.5 and 5 of the symptoms.

Diagram 1: Number of symptoms occurring at the same time, correlated with age groups

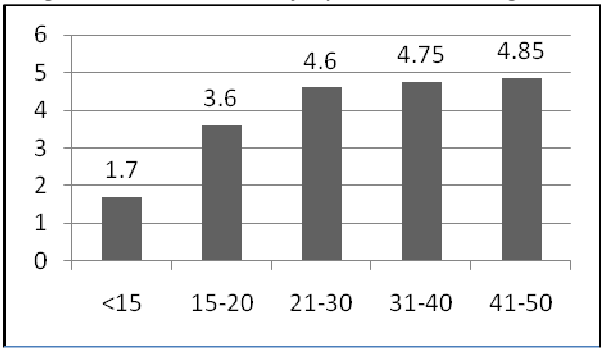
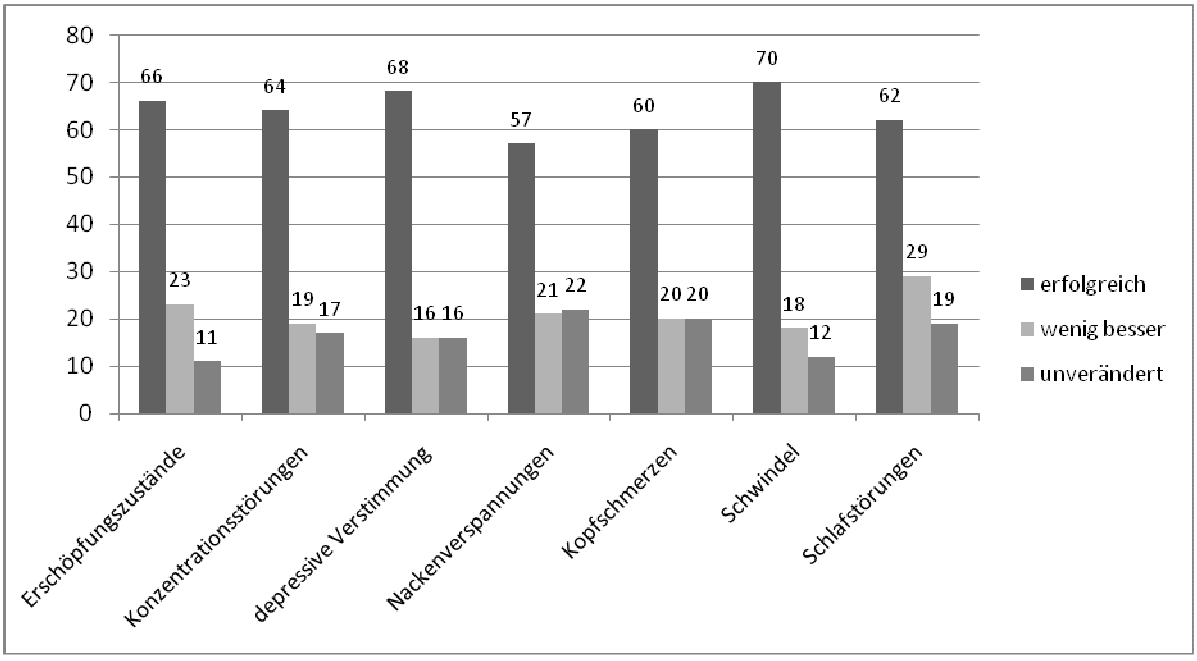


Diagram 2 shows the change in the symptoms, compiled from a questionnaire, from the patient's point of view after an individually performed loading dose of iron infusions. The fact that all symptoms have a success rate between 60 to 70% is notable. Only in the case of neck tension is the figure lower, at 57%.

Diagram 2: Success rates (in %) per symptom



The long-term effects of the treatment can be seen in **diagram 3**. It shows that the therapy success after three months has hardly decreased. The number of patients who have no symptoms or who have experienced a notable improvement in their symptoms almost remains unchanged.

Diagram 3: Success rates after the loading dose and 3 months later

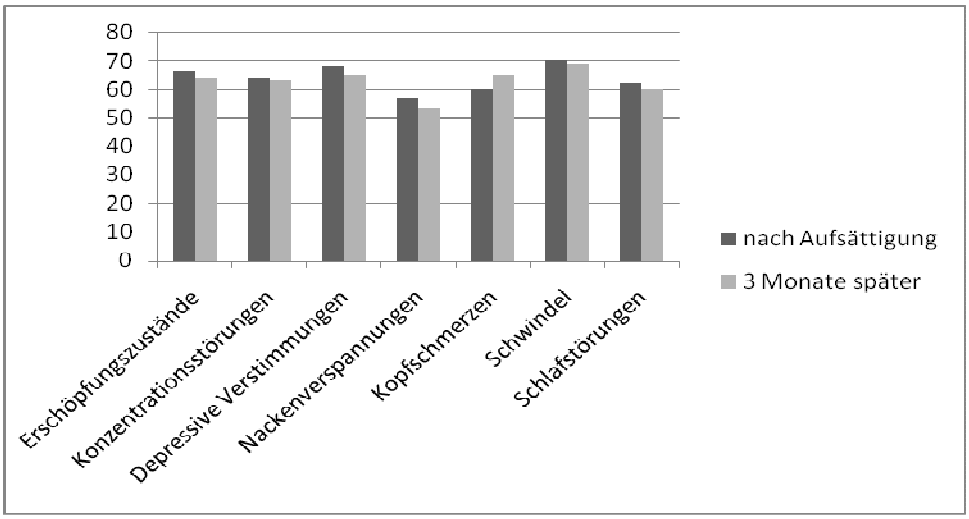
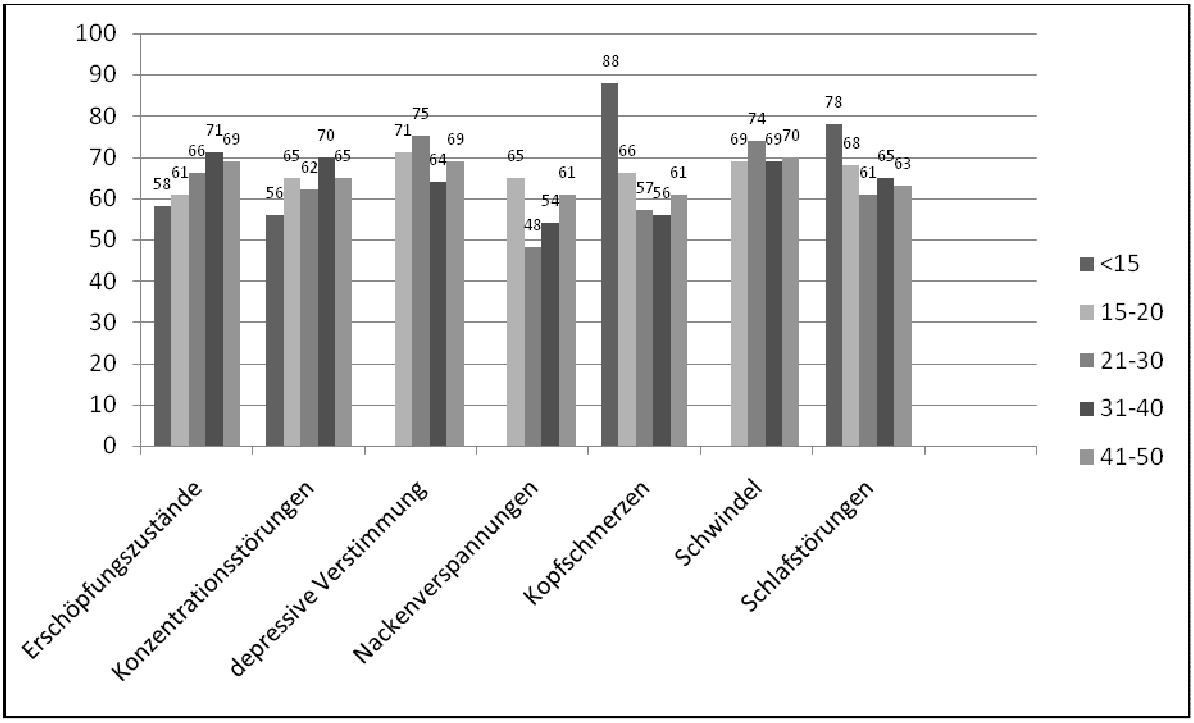


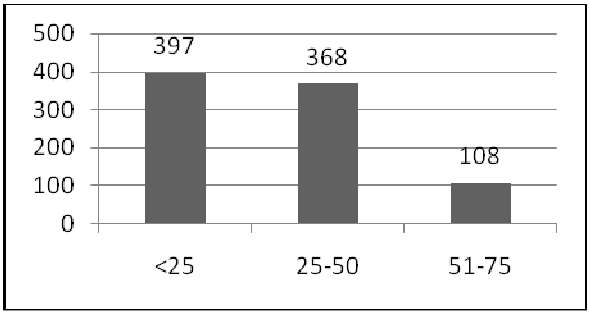
Diagram 4 reflects the distribution of success rates according to age groups. These are approximately between 50% and 70%, also within the individual age groups. What is striking is that it was possible, in particular, to successfully treat the symptoms of headaches (88%) and sleeping disturbances (78%) in the under-15s with iron replenishment.

Diagram 4: Success rates (in %) of symptoms correlated with age groups



Of the 873 patients, 88% have a ferritin value below 50 ng/ml and of these 52% have a ferritin value below 25 ng/ml (**Diagram 5**).

Diagram 5: Correlation of patient numbers with ferritin groups



From **Diagram 6** it is evident that the symptom frequency is hardly influenced by the ferritin value. However, it does indicate a dependency between the treatment success and the ferritin value: the success rates in ferritin groups < 25 and 25-50 ng/ml are comparable and are roughly between 60% and 70%. In the case of patients with a ferritin content of between 51-75 ng/ml, the treatment success of individual symptoms is, however, on average 10% lower. For neck tension, there are actually over 20% fewer patients who could be successfully treated (**Diagram 7**).

Diagram 6: Frequency of symptoms (in %) correlated with ferritin groups

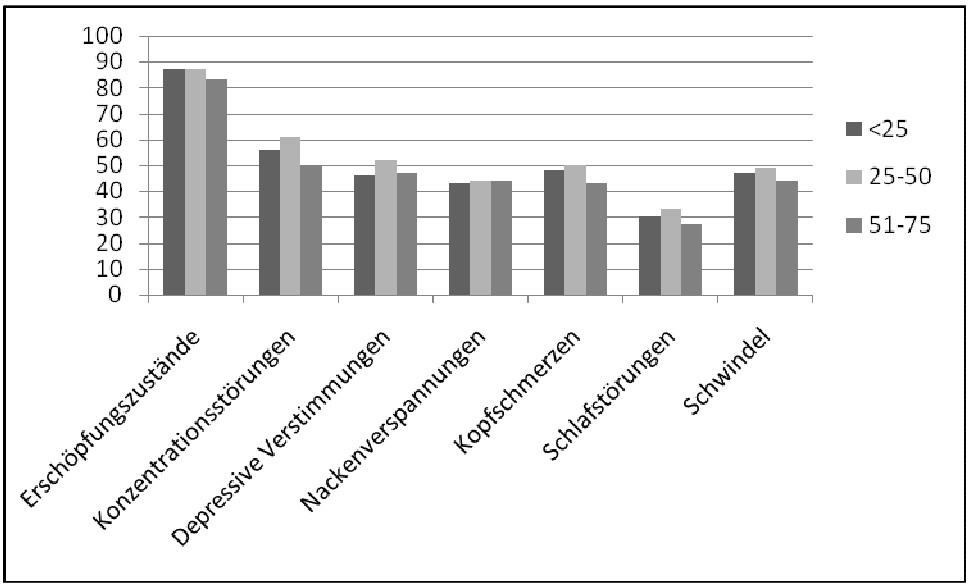


Diagram 7: Success rates (in %) according to ferritin groups

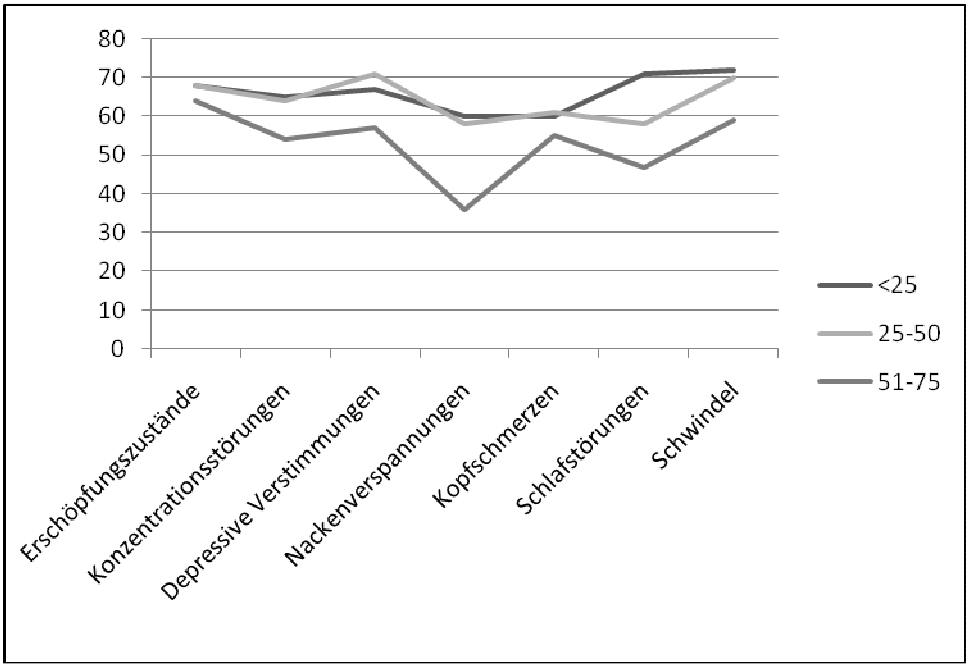
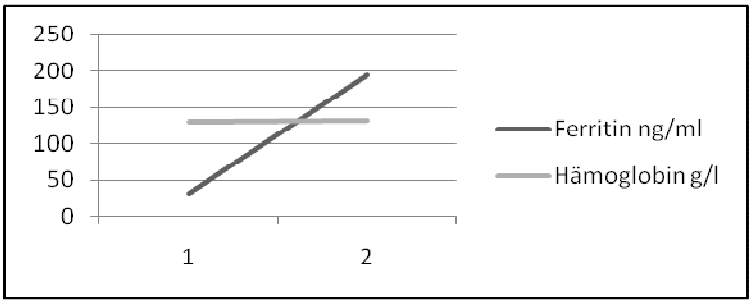


Diagram 8 shows the change in laboratory values as a result of treatment. Before the intravenous loading dose, the ferritin value was on average 31 ng/ml, afterwards 194 ng/ml (target value of Internet calculator: 200). The hemoglobin value rose during this time from 130 g/l to 131 g/l.

Diagram 8

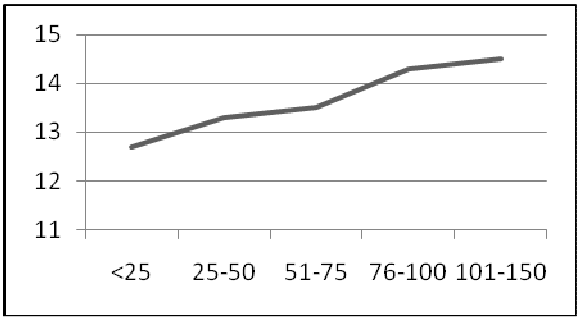


Side effects:
Of the 873 patients treated, 38 (4.4%) suffered slight temporary and undesirable side effects (most frequently tiredness, stomach/intestine problems, skin rashes, painful joints, dizziness). There were no anaphylactic reactions.

Iron Deficiency Syndrome IDS and Iron Deficiency Anemia IDA:
Of the 873 patients only 14% (114) had anemia (Hb < 12.0 g/dl), of which 73% of the cases were successfully treated with iron infusions (highest success rate in age group < 15 years).
79 (69%) of the 114 anemic patients had a ferritin value of < 25, the other 35 (31%) had a ferritin value of between 25 and 50.

There was no anemia present in 86% of the patients, although the ferritin value for roughly half of them (397 n) was under 25 ng/ml. **Diagram 9** shows the correlation between hemoglobin and ferritin values. What is striking is the fact that in cases where the ferritin value was below 25 ng/ml, the hemoglobin is, on average, at the lower end of the standard range, yet still lies in the reference range as defined up to now. This is an indication that the official lower standard value is generally sufficient to prevent an anemia.

Diagram 9: Correlation between ferritin groups and average hemoglobin



Discussion

The results of this multicentre drug monitoring study show that in the case of nearly all the patients (including the children) who had symptoms such as fatigue, difficulty concentrating, depressed moods, headaches and neck pains, the ferritin value was below 50 ng/ml (in almost half of these cases, it was between 25 and 50 ng/ml) - i.e. a range which is defined as normal by most laboratories, and for which reason, according to medical opinion, no iron treatment at all would have been required up to now.
Contrary to previous assumption - on the basis of the findings from 2006 (1) - these patients were diagnosed as iron deficiency patients and were treated with iron infusions according to their individual requirements.

The overall high success rate of roughly 60-70% (depending on the symptom), both directly after iron replenishment and 3 months afterwards, indicates that depleted iron stores (ferritin values below 50 ng/ml), even without presence of an anemia, can lead to symptoms.

In light of the huge (68%) treatment success with intravenous iron infusions in the cases of ferritin values below 50ng/ml for depressed moods and taking into consideration the recently published meta analysis (3), which questions the effectiveness of the top-selling SSRI, we doctors should ask ourselves maybe from a different viewpoint about the causes of an endogenous depression. The answer "depleted iron stores" seems obvious and should be investigated more closely.
Because by an effective supply of the lacking iron, the metabolic functions are reactivated, which, up to now, were reduced to a minimum. Since roughly 50% of depressed people have depleted iron stores and, therefore, produce insufficient endorphins, it is recommended that the ferritin value must first be measured and afterwards - in the event of depleted iron stores - iron be given as the top priority.

This drug monitoring study further shows that low ferritin values can already cause complaints in childhood and whose frequency is doubled up until age 20 and thereafter remains approximately constant. This study suggests that symptoms, which are obviously the result of low ferritin values,

should be treated at an early stage before the symptoms increase. In children, the most frequently occurring iron deficiency symptoms such as fatigue, difficulty concentrating and sleeping disturbances, as well as headaches, point towards an ADD. Thus the obvious assumption is that an attention deficit disorder is often the result of a lack of iron. The question about the causes of an ADD should therefore be revisited. Before Ritalin is prescribed, it would perhaps be advisable to determine the ferritin value and, if necessary, to first replenish the iron stores.

A ferritin value between <25-75 ng/ml has hardly any influence on the type and frequency of symptom development. The treatment success is, however, influenced decisively by the ferritin value. In the case of ferritin values between 50 and 75 ng/ml the therapy success is constant up to over 20% less than in the case of ferritin values below 50 ng/ml. On the one hand, this study suggests that ferritin values above 50 ng/ml are approaching the physiological "minimum value" and/or, on the other hand, that in the case of patients with a higher ferritin value, i.e. between 50-75ng/ml, other causes are still present.

The fact that only 14% of the 873 iron deficiency patients were identified as anemic proves that the diagnosis of iron deficiency is in no way dependent on anemia. This is only the case in iron deficiency anemia.
Also in the case of a ferritin value of 25 ng/ml, the average value for hemoglobin is normal for 86% of patients, although many patients suffer complaints - even without anemia.
The results of this monitoring study clearly indicate that the standard values for ferritin must be reconsidered and redefined.
Up to now, the acknowledged and officially advocated lower standard value for ferritin is sufficient in most cases to prevent an anemia. Subjective mental states such as depressed moods, difficulty concentrating, sleeping disturbances etc. can already appear in the case of ferritin values below 75 ng/ml. In light of the fact that not only an anemia is to be prevented, but also that patients have a right to a cure of other symptoms caused by iron deficiency, we are suggesting an increase in the lower standard value of ferritin to at least 50 ng/ml.

The results of this investigation are impressive, even if their significance has not been supported with statistical tests so far. However, from a purely scientific point of view, the merely descriptive evaluation of the data is a weakness of this practical report. Controlled studies, which are currently being performed at the universities of Zurich and Basel, are necessary to scientifically confirm the effectiveness of iron as indicated in this monitoring study.

Conclusion

1. This study proves that Iron Deficiency Syndrome IDS exists and that this syndrome can be successfully treated.

2. The high treatment success (68%) with iron in the case of ferritin values below 50 ng/ml and depressed moods, on the one hand, and the recently published meta analysis (3), which questions the effectiveness of the top-selling SSRI, on the other, raise the question once again about the causes of an endogenous depression.
The answer "depleted iron stores" seems obvious and should be investigated more closely.

3. Even though the number of children available for clinical research was small, one can generally conclude that children with depleted iron stores may also have symptoms of the classic attention deficit disorder ADD. The question about the causes of an ADD should thus be revisited. It would

perhaps be advisable to first determine the ferritin value and, if necessary, to replenish the iron stores before other therapies are employed.
In light of the fact that not only an anemia is to be prevented with iron infusions, but that patients also have a right to a cure of other symptoms caused by iron deficiency, we are suggesting an increase in the lower standard value of ferritin to at least 50 ng/ml.

5. Iron deficiency syndrome IDS is a widespread and well treatable problem. On the basis of the data, it is even obvious that not only IDS must be defined, but also, for example, iron deficiency depression, iron deficiency ADD and iron deficiency insomnia.

6. The online concept (Advanced IDS Management AIM) for optimal diagnosis, treatment and relapse prevention has proven itself. It allows not only the administration of an individually optimum loading dose, but also quality management, which makes it possible to constantly optimize the AIM.

7. The treatment costs are relatively high, in most cases, however, lower compared with previous procedures and attempted therapies that yielded little or no success. With the re-introduction of iron carboxymaltose (Ferinject), treatments could be administered with considerably less expense, whereby the costs would decrease by roughly half. Thus the need for a comparative drug-monitoring study of Ferinject versus Venofer becomes apparent. It remains to be hoped that the new medicine Ferinject has the same effectiveness and is as well tolerated as Venofer so that in the future nothing stands in the way of inexpensive treatments.

Literature

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