Reduced iron parameters and cognitive processes in children and adolescents with DM1 compared to those with standard parameters

Ewa Mojs,[1] Maia Stanisławska–Kubiak,[1] Rafał W Wójciak,[1] Julita Wojciechowska,[2] Sabina Przewoźniak[3]

[1]Department of Clinical Psychology, Poznan University of Medical Sciences, Poznań, wielkopolskie, Poland
[2]Department of Psychology, Adam Mickiewicz University, Poznan, wielkopolskie, Poland
[3]Department of Paediatric Diabetes and Obesity, Poznan University of Medical Sciences, Poznan, Poland

Correspondence to
Dr Maia Stanisławska Kubiak, Poznan University of Medical Sciences, Bukowska 70, Poznań 61-780, Poland; maiakubiak@gmail.com

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ABSTRACT

Anemia in patients with diabetes is not scarce and may contribute to the complications of the disease. The risk of iron deficiency parameters in child sufferers of diabetes type 1, observed in studies, can lead to cognitive impairment. The aim of the study was to determine whether children and adolescents with diabetes type 1, in whom reduced ferric parameters are observed in control tests, may also show reduced cognitive performance. The study included 100 children with diabetes type 1 at the age of 6–17 years. During control tests, patients' morphological blood parameters were measured: red blood cells (RBC), hemoglobin, glycosylated hemoglobin, hematocrit, RBC volume, the molar mass of hemoglobin in RBC (MCH), mean corpuscular hemoglobin in RBC and iron concentrations in serum using flame atomic absorption spectroscopy and the Wechsler Intelligence Scale for Children (WISC-R). Results in the group of children with a diabetes type 1 significantly lower concentration of three ferric parameters affect the non-verbal intelligence measured with WISC-R. The prevalence of reduced ferric parameters justifies further screening in all children with diabetes type 1 and taking up appropriate preventive measures to reduce the risk of their occurrence.

Significance of this study

What is already known on this subject?

- Research work progressively more often shows that anemia in young children causes difficulties in the development of cognitive processes and may even lead to mental retardation.
- Iron deficiency anemia can also be a risk factor for normal cognitive development in children with type 1 diabetes.
- The risk of iron deficiency parameters in children suffering from type 1 diabetes can lead to cognitive impairment and may contribute to the pathogenesis of diabetes complications.

What are the new findings?

- There are relatively few studies on the occurrence of iron deficiency and intellectual functioning in children with type 1 diabetes.
- Increasingly, research work reports that anemia in young children causes difficulties in the development of cognitive processes and can even lead to mental retardation. Iron deficiency anemia can be a risk factor for normal cognitive development in children with type 1 diabetes.
- Iron deficiency impairs the metabolism of neurotransmitters and also impairs the transport and storage of oxygen, thus negatively affects the function of the central nervous system and cognitive abilities of a child.

How might it impact on clinical practice in the foreseeable future?

- The occurrence of reduced iron parameters stands for a good reason of screening all children with type 1 diabetes and to take appropriate preventive measures to reduce the risk of occurrence.
- Implementation of the treatment of anemia in patients with type 1 diabetes reduces fatigue, and improves cognitive function and the ability to work, which affects the psychosocial development of children with type 1 diabetes.

INTRODUCTION

Diabetes type 1 is an autoimmune disease which belongs to the group of the most frequently diagnosed chronic diseases among the population of children and adolescents. Most research shows a steady increase along with lowering of the age of incidence (less than 5 years) for diabetes type 1. The aims of treatment of diabetes in children require a number of specialized operations (optimization of blood glucose levels during the day, which minimizes the occurrence of hypoglycemia and hyperglycemia, maintenance of normal blood pressure, with glycosylated hemoglobin (HbA1c)≤ 6.5%, normal total cholesterol, and the like.).[1] According to studies, factors operating in diabetes increase the risk of many disorders of bodily functions including anemia and cognitive disorders. Thomas *et al* (2003) and other authors[2 3] are of the view that, anaemia,

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frequent in diabetes, potentially contributes to the pathogenesis of diabetic complications. In addition, anemia in diabetes may be more common[2] and increase the development of renal impairment.[3] The study by Bennett and Magnus[4] shows that 15% of women and 13% of men with diabetes type 1 also suffer from anemia. For comparison, the incidence of anemia in the non-diabetic Caucasian population of the same age is less than 2% in men and less than 6% in women.[4]

Iron plays an essential role in hemoglobin synthesis and electron transport for cellular respiration, DNA synthesis, and other important enzymatic reactions. Early detection and treatment of iron deficiency and conditions that predispose to this deficiency can significantly reduce mortality in patients with diabetes.[5] There are relatively few studies on the prevalence of iron deficiency and intellectual functioning in children with diabetes type 1. Therefore, there is a threat that the risk of anemia may remain undiagnosed and/or untreated. This is further complicated by the lack of systematic monitoring of anemia in children with diabetes, especially in the absence of overt nephropathy (characteristic of most young patients). Implementation of treatment of anemia in patients with diabetes type 1 leads to fatigue reduction, improves cognitive function, and ability to work,[6 7] which influences the psychosocial development of children with diabetes type 1. Thus, the aim of the study was to determine the association between diabetes type 1, lowering ferric parameters and cognitive functioning.

MATERIALS AND METHODS

The study was conducted on 100 children, 55 girls and 45 boys with diabetes type 1, in the age group 6–17 years (11.95±2.85). All patients were under the care of the Clinic for Diabetic Children in Poznan, and in the course of the study, they were periodically hospitalized in the Clinic of Diabetes and Obesity for Children and Adolescents, Poznan University of Medical Sciences within the framework of routine control tests established for these patients. Patients qualified for the research did not suffer, apart from diabetes type 1, from other conditions that could affect the results, such as thyroiditis, malabsorption, epilepsy, etc. Participation in the study did not impair the therapeutic treatment during hospitalization. The study was approved by the Ethics Committee of the Poznan University of Medical Sciences. Parents of patients were informed about the study and gave their consent. Blood samples were taken from the children's brachiocephalic vein; then the blood morphological parameters were measured (red blood cells (RBC), hemoglobin (HGB), hematocrit (HCT), RBC volume (MCV), the molar mass of hemoglobin in RBC (MCH), mean corpuscular hemoglobin in RBC (MCHC), HbA1c) as part of standard clinical procedures. Reference ranges were as follows: RBC 4.00–5.20 M/µL; HGB 11,5–15.5 g/dL; HCT 35.0–45.0%; MCV 76–91 fL; MCH 25.0–32.0 pg; MHCH 28,0–33.0 g/dL; Fe 50–175 mol/dL; HbA1c> 6,5%. In addition, serum was extracted from the sample using Flame atomic absorption spectroscopy (FAAS) and the iron concentration was determined (AAS-3, Zeiss, Jena). In order to assess cognitive functioning, the Wechsler Intelligence Scale for Children (WISC-R) was used, which allows for an objective assessment of the efficiency of different cognitive areas such as intelligence, verbal and executive functions, memory and attention and learning processes. The results obtained are presented in accordance with standard guidelines of descriptive statistics as SD, variance and range. All results were subjected to statistical analysis using Student's t test $p<0.05$.

RESULTS

The mean results of IQ, verbal and executive functions and various cognitive functions included in intelligence, considered along with ferric parameters, are shown in table 1. In the group of 100 children with diabetes type 1, 12 children presented at least three lowered blood morphological parameters: RBC, HGB, HbA1c, HCT, MCV, MCH, MCHC and iron concentrations in serum using FAAS. The lowered reference ranges were measured as follows: RBC 4.00–5.20 M/mL; HGB 11,5–15.5 g/dl; HCT 35.0–45.0%; MCV 76–91 fL; MCH 25.0–32.0 pg; MHCH 28,0–33.0 g/dL; Fe 50–175 mol/dL; HbA1c> 6.5%. Diabetes duration in the group was as follows: for children with reduced iron parameters—2.58 years, for the remaining participants—4.78 years, which poses a statistically significant difference (table 1).

IQ scores as well as the separate scales included in intelligence are presented in table 1. All the mean indications for the areas that form the general IQ in the examined group of patients fall within the range of average and above average intelligence level. While comparing the group with reduced ferric parameters and the one of children with iron results in meeting standard parameters, significantly lower scores in the non-verbal intelligence (NI) performance and the coding subtest were achieved by a population with lower ferric parameter values (table 1). NI scores in the group with normal ferric results are 112, whereas in the group with reduced ferric parameters the score is 102. IN indicates the level of non-verbal capabilities based on the child's ability to solve new problems. In the coding subtest, in the group of children with normal results, the mean score was 12, and in children with reduced parameters it was 9. Coding is a subtest measuring the eye-hand coordination, perception of abstract stimuli, and psychomotor speed.

DISCUSSION

Although the scores of cognitive functioning presented by all the children are within the standard range for the age, the study indicates that children and adolescents suffering from diabetes type 1 with lowered ferric parameters may get lower scores in non-verbal subtests compared with those with normal parameters.

The problem of iron deficiency anemia in children with diabetes was presented in the article by Wójciak *et al*.[8] They show that significantly lower concentrations of at least three of the blood parameters are supposedly associated with iron deficiency anemia in children, may vary over the duration of the disease, and affect up to 26% of children.[8] Clearly visible here is the changing clinical picture of iron deficiency in type 1 diabetes, different in children and adults, and different in the course of the disease.

This study shows that the most vulnerable moment of iron deficiency in children with diabetes may be the moment of diagnosis and the first years of the disease.[8] According to Tarim *et al*[6] and Cody *et al*[7], iron deficiency

Table 1 Comparisons of cognitive and biochemical statistics for groups with three indicators of iron deficiency parameters and those without deficiencies*

	Iron deficiency parameters	N	Arithmetic mean	SD	SE of the mean
Verbal intelligence	NO	88	108.10	15.48	1.65
	YES	12	109.75	15.93	4.60
Non-verbal Intelligence	NO	88	**112.32 a**	14.40	1.53
	YES	12	**102.92 a**	13.81	3.98
IQ Full-scale IQ	NO	88	111.15	14.63	1.56
	YES	12	107.92	14.95	4.32
Information	NO	88	9.60	3.33	0.35
	YES	12	10.42	3.63	1.05
Similarities	NO	88	12.26	2.67	0.28
	YES	12	12.75	3.39	0.98
Arithmetic	NO	88	10.95	3.12	0.33
	YES	12	11.83	3.35	0.97
Vocabulary	NO	88	10.93	3.05	0.32
	YES	12	10.08	2.68	0.77
Comprehension	NO	88	12.33	3.25	0.35
	YES	12	12.67	2.74	0.79
Number Sequencing	NO	88	10.45	2.98	0.32
	YES	12	10.08	3.15	0.91
Picture completion	NO	88	9.96	2.73	0.29
	YES	12	9.33	2.39	0.69
Picture concepts	NO	88	12.81	3.55	0.38
	YES	12	11.67	3.23	0.93
Block design	NO	88	11.92	2.89	0.31
	YES	12	10.59	2.35	0.68
Puzzles Matrix Reasoning	NO	88	11.61	3.59	0.38
	YES	12	10.83	3.61	1.04
Coding	NO	88	**12.44 b**	3.04	0.32
	YES	12	**9.58 b**	1.93	0.56
Disease duration	NO	88	**4.80 c**	3.48	0.37
	YES	12	**2.58 c**	3.92	1.13
HGB	NO	88	**13.88 d**	1.08	0.12
	YES	12	**11.82 d**	2.03	0.59
HCT	NO	88	**39.54 e**	3.05	0.33
	YES	12	**33.68 e**	4.08	1.12
RBC	NO	88	**4.75 f**	0.39	0.042
	YES	12	**4.13 f**	4.13	0.12
MCV	NO	88	83.49	5.21	0.56
	YES	12	81.08	8.53	2.46
MCHC	NO	88	35.10	1.04	0.11
	YES	12	34.91	3.03	0.87
MCH	NO	88	29.30	1.70	0.18
	YES	12	28.30	3.68	1.06
HbA1C	NO	88	9.92	2.44	0.29
	YES	12	9.52	2.05	0.72
Iron, mol/dL	NO	88	108.47	34.62	3.69
	YES	12	102.85	34.78	10.04
Age of onset	NO	88	7.24	3.19	0.34
	YES	12	8.92	3.37	0.97
Duration of the illness	NO	88	**4.78 g**	3.45	0.37
	YES	12	**2.58 g**	3.92	1.13
Sex	**Girls**=55 **Boys**=45				
Age	**Mean**=11.95 **Median**=12.00 **Mode**=15.00 **SD**=2.85 **Minimum**=6 **Maximum**=16				

Arithmetic mean a, b, c, d, e, f, g—statistically significant differences at <0.05.
*Individual differences identified as statistically significant for the indicated characteristics are the differences between the individuals with and without anemia.
HbA1c, glycosylated hemoglobin; HCT, hematocrit; HGB, hemoglobin; MCHC, mean corpuscular hemoglobin in RBC; MCV, RBC volume; RBC, red blood cells.

in adults with diabetes type 1 is associated with long-term disease and kidney malfunction. At the same time, Cody *et al*[7] pointed out that among patients with diabetes type 1 with a similar level of glycemia, anemia due to iron deficiency is associated with higher HbA1C levels. Our study demonstrates that lowered iron parameters may occur in children suffering from diabetes type 1 in the first 2 or 3 years (table 1).

In a cross-sectional study on patients with diabetes, Thomas *et al*[9] found that nearly a quarter of all outpatients had anemia.

Anemia can cause physical and mental disorders in diabetes, which consist of malaise, fatigue, weakness, shortened breath, as well as cognitive dysfunction and other symptoms. There is evidence that anemia in patients with diabetes contributes to retinopathy, neuropathy, diabetic foot ulcers, hypertension, kidney disease and cardiovascular disorders, etc.[9–13]

The iron in the body is involved in the production of hemoglobin and myoglobin, but also plays an important role in the work of many enzyme systems and cytochromes in electron transport, for example, in the formation of the myelin in the developing brain.[14]

Increasingly, in the research, it is reported that anemia in young children causes difficulties in the development of cognitive processes and even leads to mental retardation.[15 16] Iron-deficiency anemia can also be a risk factor for cognitive development in children with diabetes type 1.

Walter[17] suggests that iron deficiency impairs the metabolism of neurotransmitters and the transport and storage of oxygen and thus negatively affects the function of the central nervous system and cognitive abilities of the child. Pollitt *et al*[18] note that low mental development test results and attention deficits may be due to iron deficiency.

Clinical descriptions of anemia in children focus on their irritability, apathy, and lack of appetite, and the results show impaired psychomotor development,[19] which also corresponds to the results of this work, in which statistically significant cognitive deficits are evident in the non-verbal/executive functions that is, related to the development of hand-eye coordination, work dynamics, and functions of fine motor skills within IQ.

CONCLUSIONS

The analysis above is important for cognitive function testing, as it is difficult to underestimate the effects of iron deficiency on the occurrence of cognitive disorders and, possibly, motor dysfunctions, since it concerns 12% of the checked children.

Verification of hypotheses concerning the relationship between iron deficiency and the development parameters of cognitive processes supposedly showed that significantly lower scores in the development of NI and coding subtests are gained by participants in whom at least three decreased iron parameters were observed.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The Poznan University of Medical Sciences, Poland.

Provenance and peer review Not commissioned; externally peer reviewed.

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