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Type 1 Diabetes Mellitus presenting as neurodevelopmental impairment

Marta Faria Alves[I], Mónica Costeira[I], Joana da Silva Ferreira[I], Susana Soares[I], Catarina Magalhães[I], Carla Meireles[I]

ABSTRACT

Introduction: Type 1 Diabetes Mellitus is one of the most prevalent chronic diseases in childhood and adolescence. Disease presentation is diverse, depending on the duration of symptoms and the age of onset.

Case report: A 30-month-old child was referred to the Paediatric Outpatient Clinic for loss of cognitive and behavioural skills and stagnation of motor abilities occurring in the last six months, weight loss and polydipsia during the previous month. The child was diagnosed with inaugural type 1 Diabetes Mellitus without acidosis. Management of the disease, through glycaemic control with insulin therapy was associated with progressive improvement of the child's neurodevelopment.

Discussion/Conclusion: This case illustrates an unusual presentation of type 1 Diabetes. The mechanisms underlying acute neurological changes associated with type 1 Diabetes are not yet completely clarified. An efficient glycaemic control benefits an adequate neurodevelopment of children with Diabetes.

Keywords: Child neurodevelopment; Hyperglycaemia; Type 1 Diabetes Mellitus

DIABETES MELLITUS TIPO 1 APRESENTANDO-SE COMO PERTURBAÇÃO DO NEURODESENVOLVIMENTO

RESUMO

Introdução: A Diabetes Mellitus tipo 1 é uma das doenças crónicas mais prevalentes na infância e adolescência. A apresentação da doença é variável, dependendo da duração dos sintomas e da idade da criança.

Caso Clínico: Os autores descrevem o caso de uma criança de 30 meses avaliada em consulta de Pediatria por perda de competências cognitivo-comportamentais e estagnação das aquisições motoras, tendo sido diagnosticada uma Diabetes Mellitus tipo 1 inaugural, sem acidose. Após a melhoria do controlo glicémico com a insulinoterapia, verificou-se uma normalização progressiva do neurodesenvolvimento da criança.

Discussão/ Conclusão: Este caso ilustra uma apresentação incomum da Diabetes Mellitus tipo 1. A fisiopatologia das alterações neurológicas agudas associadas à Diabetes Mellitus tipo 1 ainda não está totalmente esclarecida. Um controlo glicémico eficaz é benéfico para o adequado neurodesenvolvimento das crianças com Diabetes.

Palavras-chave: Diabetes Mellitus tipo 1; Hiperglicemia; Neurodesenvolvimento infantil

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[I] Department of Pediatrics, Hospital Senhora da Oliveira – Guimarães. 4835-044 Guimarães, Portugal.
martaalves@hospitaldeguimaraes.min-saude.pt; monicasnacosteira@gmail.com; joanaferreira.med@gmail.com; susanapediatria@gmail.com; catarinadiasmagalhaes@gmail.com; csmeireles@gmail.com

INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is the most prevalent endocrine-metabolic disease in childhood and adolescence. It is characterized by hyperglycaemia due to deficient insulin production caused by the destruction of pancreatic beta cells.

The initial manifestation in children usually includes the classic symptoms of the disease. However, the presentation of T1DM is variable and influenced by the duration of symptoms and the age at diagnosis[1]. This case reports an unusual presentation of T1DM with increased diagnostic difficulties.

CASE REPORT

A 30-month-old female child was referred to a Paediatric Outpatient Clinic for psychomotor development impairment.

Prenatal history included an increased nuchal translucency. Chorionic villus sampling revealed the fetus had a 46, XX karyotype.

The child was born with 39 weeks of gestational age by a vacuum-assisted vaginal delivery. She was well adapted to extra uterine life and had an adequate weight for gestational age. The neonatal period was uneventful and neonatal screening programme results were normal.

At the age of three months she smiled and had head control. By 8 to 9 months of age she sat unsupported, crawled by 11 months and walked independently around the age of 18 months. Her mother recalled she could manipulate toys at the age of 6 to 8 months and was able to point using the index finger soon after 12 months. At 12 months she started using common objects like spoons and she pretended to "talk" on the phone. The girl pronounced her first meaningful words at around 15 months.

At the age of two years old she could not walk up the stairs unassisted; she put two or three words together to form simple sentences; she had spontaneous circular scribble, indicated parts of her body and could feed herself with a spoon and drink from a cup; she played with dolls, holding and feeding them. At this age she could imitate domestic activities. She had not yet acquired sphincter control.

The child was taken care of by her grandfather and did not attend a day care centre.

There were no pathological personal or familial antecedents.

By the age of 25 months there was a decline in her psychomotor skills. She had an uncertain, broad-based gait, very similar to the gait pattern she had at the time of acquisition of independent walking. The child also presented an impoverishment of expressive language and an irritable mood during this period, with frequent crying and temper tantrums.

During the interview, the mother reported an approximate weight loss of 3 kilograms associated with polydipsia that had occurred within the previous month. She attributed the polydipsia to the hot summer weather, therefore it did not constitute a priority complaint during the interview.

The child had a reasonable overall condition. Mucous membranes were dehydrated and her eyes were sunken. She was afebrile.

Neurological examination showed very poor eye contact and handling of objects – she was not able to build a tower of cubes or to scribble.

The child met very simple orders with great difficulty, she did not mimic or recognize parts of the body. She had an occasional verbal language, mostly imperceptible even to her caregivers, with frequent echolalia. Stereotypies were present – clapping, hand movements and flapping of the arms. According to the mother, these movements had appeared for the first time in the previous month. The posture was symmetrical, with normal tone of the various segments. She was not able to walk up or down the stairs or to get up off the ground without support. She presented a broad-based stereotypical gait, without ataxia. The remaining neurological examination was normal, without pyramidal or cerebellar signs or other involuntary movements. At the time of the first observation, DSM-5 criteria for autism spectrum disorder were not totally met, though she presented deficits in social communication and interaction across contexts and repetitive patterns of behaviour, namely stereotyped/ repetitive speech and movements.

Faced with this clinical presentation, neurodegenerative diseases, metabolic or other systemic or neurological causes were considered. Research was initiated with a blood count and an extended biochemical profile.

The analytical study identified a normal blood count, venous blood gasometry without acidosis, serum glucose of 577 mg/dL and normal transaminases, lactate dehydrogenase, thyroid hormones, creatinophosphokinase and iron metabolism parameters. Calculated serum osmolarity was 309.06 mOsm/L.

After the diagnosis of inaugural diabetes mellitus without acidosis, the child was admitted to correct the imbalance with insulin therapy. Once she was stable a management plan for disease control was discussed with the family and she kept follow-up in Pediatric Neurology and Diabetology. The child started attending a nursery school after hospital discharge.

At 32 months the child kept reasonable glycaemic control under a multiple daily insulin injections regimen (MDI). Analytical data favoured the diagnosis of an autoimmune type 1 Diabetes: reduced levels of C-peptide (0.26 ng/ml) and positive islet cell cytoplasmic antibodies and glutamic acid decarboxylase antibodies (1/16 and 4.44 U/ml, respectively). Screening of coeliac disease was negative (negative transglutaminase and deamidated gliadin antibodies).

Despite attending nursery school, she did not engage on any developmental intervention programme and kept the neurodevelopmental changes described. Research progressed by conducting a brain nuclear magnetic resonance, which was normal.

At 33 months of age an improvement of psychomotor acquisitions was observed: she had good eye contact, showed symbolic play and had more frequent and perceptible expressive language. Abnormal movements initially described were no longer observed. She had a normal gait and was able to rise without support. The remaining neurological examination was normal.

Since the clinical situation had a probable endocrine/ metabolic cause and was already showing signs of improvement,

it was decided not to proceed with the etiological investigation and to maintain frequent clinical reassessments of the child.

During follow-up, the child presented a normal psychomotor development and neurological examination. During the three years the patient has been under treatment with a continuous subcutaneous insulin infusion system, with good metabolic control (A1c-hemoglobin 6.5%). Currently, at the age of 6 years, she attends the first grade of primary school with good academic performance, takes ballet classes and is well integrated into the peer group. She actively participates in the management of her illness.

This case represents an acute psychomotor development impairment associated with the onset of T1DM, with favourable clinical evolution.

DISCUSSION

Diabetes mellitus is a heterogeneous syndrome, involving multiple differential diagnoses.[1] Although it mostly occurs as T1DM in the paediatric age (95% of cases), this case presentation led to the consideration of other types of Diabetes Mellitus (DM).

Because of the association between DM and neurobehavioural changes, some differential diagnoses were considered in this case: psychomotor development dysfunction associated with the onset of T1DM, other types of DM (mitochondrial diabetes or DM associated with genetic syndromes) or the occurrence of two independent diseases (T1DM and another condition, which would explain the neurobehavioural changes).

The endocrine system and the central nervous system are closely related in the maintenance of homeostasis. Acute and potentially reversible neurological manifestations have been associated with T1DM, including altered mental status and movement disorders. Altered mental status in T1DM occurs primarily in the setting of diabetic ketoacidosis (the most serious neurological manifestation being acute cerebral oedema) or hypoglycaemia, both situations often related to a rapid correction of a hyperglycaemic and hyperosmolar state.[2] As for movement disorders in this context, there are descriptions of chorea-ballism. These situations are very rare in children and in T1DM and they are reversed or improved by hyperglycaemia correction.[3-5]

Although it is virtually possible that any systemic disease may affect psychomotor development, there is limited data about this subject, so it is relevant to discuss the effects of hyperglycaemia in the central nervous system and the relationship between T1DM and psychomotor development.

The brain´s main energy source is glucose. In the blood-brain barrier glucose transport is performed mainly by GLUT1 transporter through a diffusion process.[6] Modifications in this transporter structure/function have been implicated in neurologic diseases.[6,7] Glucose transport by GLUT1 is insulin independent, so glucose, and not insulin, could be responsible for neurological disorders associated with DM. Neurons dependence on the extracellular concentration of glucose makes them inefficient in inhibiting glucose transport into the intracellular environment, putting these cells at a higher risk of toxicity in extreme glycaemic fluctuations.[6,7]

In hyperglycaemic environments the expected response would be a GLUT1 decreased expression/activity for neuronal protection. However, results have been conflicting: in some studies there were no changes in GLUT1 expression/activity in hyperglycaemic environments, so an adaptive response may not occur, exposing neurons to excessive glucose levels.[6]

Some neuronal injury mechanisms related to hyperglycaemia have been described, namely the polyol pathway, non-enzymatic glycation and increased oxidative stress.[9,10]

Not only neurons but also glial cells appear to be a target of hyperglycaemia. Diminished glutamate uptake (the major excitatory neurotransmitter in the central nervous system) by astrocytes in hyperglycaemic environments was observed, leading to increased neuronal exposure to this neurotransmitter.[11] This leads to an excessive neuronal influx of calcium, which activates proteases, phosphatases and phospholipases, resulting in increased production of reactive oxygen and nitrogen species, with subsequent neuronal dysfunction.[11]

Apart from glycaemic fluctuations, DM also induces changes in endocrine (insulin, C-peptide, cortisol, IGF-1) and paracrine factors (ketone bodies, lactate), which may have complex effects on the central nervous system.[7]

An altered glucose metabolism may have medium and long term impact on psychomotor development, although this relationship needs further investigation.

Synaptic connections density rises dramatically during the postnatal period and remains high during childhood, decreasing from adolescence to reach adulthood levels. The evolution of glucose metabolism and oxygen consumption in the brain follows a similar pattern. This suggests that the occurrence of extreme glycaemic fluctuations, particularly at the early stages of life, may have a negative effect on psychomotor development.[8]

Some studies have evaluated structural and metabolic brain changes associated with extreme levels of blood glucose in children with T1DM[8]. While hypoglycaemia was associated with subtle hippocampal volumetric changes, hyperglycaemia was shown to have an effect on the volume of cuneus/precuneus region.[8] Spectroscopy studies found decreased N-acetyl aspartate levels in frontal lobes and basal ganglia (suggesting neuronal loss) and increased choline levels (suggesting an increased cell membranes turnover) in hyperglycaemic environments.[8] Despite these evidences, it was not possible to demonstrate a correspondence between structural/metabolic changes and functional modifications (cognitive, academic or occupational).

Prospective studies have shown worse neurodevelopment results in children with T1DM compared to healthy controls, particularly in some domains namely attention, processing speed, long term memory and executive functions.[12,13] Persistent hyperglycaemia led to inferior results in working memory, while recurrent severe hypoglycaemia led to inferior verbal scores and worse global mental efficiency.[12,13].

CONCLUSION

This case prompts reflection on the pathophysiology of acute/subacute neurological changes associated with T1DM,

which are not yet absolutely clarified. This report illustrates the close relationship between the endocrine and neurological systems, with dysfunction of one dependent on the other. Glycaemic fluctuations that occur in T1DM seem to have an impact on child development, however there is still scarcity of prospective studies on this subject. An effective metabolic control enables long-term benefits in the neurodevelopment of children with T1DM.

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CORRESPONDENCE TO
Marta Alves
Department of Pediatrics
Hospital Senhora da Oliveira – Guimarães
Rua dos Cutileiros, Creixomil
4835-044 Guimarães
Email: martaalves@hospitaldeguimaraes.min-saude.pt

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