

## Coexistence of type 1 diabetes mellitus, autism and blindness – narrative review and case report

Katarzyna Cyranka, Dominika Dudek, Maciej Pilecki, Bartłomiej Matejko, Maria Nowina-Konopka, Sabina Krzyżowska, Maciej T. Małecki, Tomasz Klupa

### Abstract

The paper presents a case of 25 female patient, who is a clinical example of a triple comorbidity – she was a preterm child in which at the age of 2 autism spectrum disorder (ASD) was diagnosed, and at the age of 3 type 1 diabetes mellitus (T1DM). The described case is special because autism coincides not only with diabetes, but also with blindness due to retinopathy of prematurity. In such a situation, the choice of the right treatment method has become a clinical challenge.

Considering the patients' health status and life conditions (comorbidity of T1DM, autism and blindness, abusive, not engaged father, difficult financial situation) very good treatment results as far as T1DM is concerned were achieved: her HbA1c values available from last 3 years ranged from 6.5-7.3%. Also, regardless of many obstacles and life crises, the patient maintains possibly the best in her conditions, psychological well-being.

The paper can be a source of knowledge and inspiration, presenting challenges and possibilities in treatment of people with T1DM, autism, and other comorbidities. From the therapeutic point of view, it indicates that well planned, individualized therapy may be the basis for creating optimal conditions for the development and improvement of the quality of life of patients.

### THEORETICAL BACKGROUND

Autism spectrum disorder (ASD) is an early onset neurodevelopmental condition defined in the DSM-5 by alterations in social communication and interaction in conjunction with repetitive, inflexible behaviors and circumscribed interests causing significant impairment in major life areas and reduced quality of life [1, 2]. Although there is wide recognition that ASD has multiple causes, both ge-

netic and environmental in origin, precise understanding of the exact mechanisms underpinning atypical neurodevelopment is lacking [3].

The estimated prevalence rate of autism is approximately 1% worldwide [4], with a higher prevalence among males than females. The widely reported male-to-female ratio for autism prevalence is 4–5:1 but large-scale, population-based epidemiological studies suggest that the ratio is in fact lower, at 3–4:1. The higher rates of autism among males reflect sex and gender differences in the likelihood of developing autism and potential gender biases in clinical assessment and diagnoses [4–6].

ASD is a group of heterogeneous syndromes with complex etiology. Researchers and clinicians now agree that a number of biological factors lie at the root of autism. Psychosocial fac-

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Katarzyna Cyranka<sup>1,2,3</sup>, Dominika Dudek<sup>1,3</sup>, Maciej Pilecki<sup>1,3</sup>, Bartłomiej Matejko<sup>2,3</sup>, Maria Nowina-Konopka<sup>4</sup>, Sabina Krzyżowska<sup>2</sup>, Maciej T. Małecki<sup>2,3</sup>, Tomasz Klupa<sup>1,2,3</sup>:<sup>1</sup>Department of Psychiatry Jagiellonian University Medical College, Kraków, Poland; <sup>2</sup>Department of Metabolic Diseases Jagiellonian University Medical College, Kraków <sup>3</sup>University Hospital in Krakow, Poland; <sup>4</sup>Faculty of Management and Social Communication Jagiellonian University Kraków

tors may increase the importance of biological variables or affect the effectiveness of treatment and rehabilitation.

A large percentage of publications implicated an association between ASD and immune dysregulation / inflammation (416 out of 437 publications, 95%), oxidative stress (all 115), mitochondrial dysfunction (145 of 153, 95%) and toxicant exposures (170 of 190.89%). The strength of evidence for publications in each area was computed using a validated scale. The strongest evidence was for immune dysregulation / inflammation and oxidative stress, followed by toxicant exposures and mitochondrial dysfunction. In all areas, at least 45% of the publications were rated as providing strong evidence for an association between the physiological abnormalities and ASD [7]. On the basis of the high-heritability index, geneticists are confident that autism will be the first behavioral disorder for which the genetic basis can be well established.

New technology, especially array chromosomal genomic hybridization, has both increased the identification of putative autism genes and raised to approximately 25%, the percentage of children for whom an autism-related genetic change can be identified [8].

Many of these factors may be the product of the combination of several underlying pathophysiological processes, such as the negative effects of imbalanced fetal sex hormone exposure during critical time windows on gene transcription and expression, and subsequent neurotransmitter, neuropeptide, or immune pathways [3, 10].

The current literature suggests that autistic girls/women tend to have more overall physical health challenges and lower overall health and quality of life than do autistic boys/men [4, 11].

A huge systematic review that included 3366 preterm infants from 18 studies revealed that when diagnostic tools were used, the overall prevalence rate of ASD was 7%. The rate is considerably higher than in the general population, in which the overall prevalence has been reported to be 0.76%. This may suggest correlation between preterm birth and further ASD development [10].

There is increasing evidence that gastrointestinal and metabolic/nutritional conditions, including obesity and diabetes have a high fre-

quency of co-occurrence in autistic individuals. These conditions could involve shared etiological mechanisms with autism as well as with life experiences (e.g., lifestyle, health care support, medication use) of autistic people [4]

Some studies suggest that the comorbidity of autism spectrum disorder in children with type 1 diabetes is greater than that in the general population [13-15]. Like type 1 diabetes, both immune-mediated and genetic factors have been implicated in the development of autism [1].

Certain factors may account for this finding, including a common autoimmune pathogenesis. In 1971, Money et al. [2, 16] reported a possible association between autism and a family history of autoimmune disease in a case report. Denney et al. [2, 17] reported a lower percentage of helper-inducer cells and a decreased helper-to-suppressor cell ratio in children with autism, and a lower percentage of lymphocytes expressing bound interleukin-2 receptors, following mitogenic stimulation compared with control subjects. These findings were inversely related to the severity of autistic symptoms. Gupta et al. [2, 18] presented findings that suggest that an imbalance of Th1 – and Th2-like cytokines may be important in the pathogenesis of autism. Plioplys et al. [2, 19] showed that in 11 of 17 patients with autism had findings suggestive of “incomplete activation” of T-cells, a finding also seen in autoimmune diseases. Comi et al. [2, 20] indicated an increased incidence of autoimmune diseases in mothers of patients with autism compared with control mothers. Furthermore, autoantibodies implicated in autoimmune thyroid disorders are found with an increased prevalence in patients with type 1 diabetes [2, 21-23]. Because youth with Type 1 diabetes visit a healthcare provider more frequently than healthy youth, one would expect that ASD might be diagnosed more often in youth with Type 1 diabetes. However, at 1.58%, the frequency of ASD in T1DM participants was similar to the general US population rate of 1.69% [21].

Autism itself is a challenging condition for the family, however the situation becomes much more difficult when there is a comorbidity of conditions. Mothers and fathers of children with ASD carry a huge caregiving burden in the form of objective difficulties, subjective distress, and symptoms of depression and anxiety. Caregiv-

ers of children with both T1DM and ASD face unique challenges, distinct from those faced by caregivers of individuals who have either disorder alone [24-28].

## THE CASE

The paper presents a 25 y.o female patient, with comorbidity – she was a preterm child in which at the age of 2 ASD was diagnosed, and at the age of 3 – T1DM. Autism coincides not only with diabetes but also with blindness due to retinopathy of prematurity.

The patient was born in 1996. Her only caregiver, mother, was born on in 1953. The mother was also born as preterm child, with a birth weight of 1,7 kg.

The patient was born in 32<sup>th</sup> week of pregnancy with birth weight 900 g and 1 point on the Apgar scale. According to the mother, the cause of premature delivery was perinatal infection and too late termination of pregnancy. The mother reports that she probably “walked with an infected pregnancy for a few days”, however, she has no medical record from that time. After giving birth, she was unconscious for a week, and therefore had no contact with her daughter. The patient was not placed in an incubator, because the local hospital where she was born lacked the appropriate equipment – the only incubator was occupied by another premature baby. After two months of hospitalization both mother and the newborn child women were released home.

At home the mother noticed, that the baby did not react to toys and movements. After consultation with ophthalmologist it turned out that she is blind. She was then hospitalized in Children’s Health Center and diagnosed with retinopathy of prematurity. She underwent an operation to restore at least partial vision, during which she experienced clinical death. The operation itself was unsuccessful and as a complication the eyeballs were atrophied, the color-receiving cells were damaged and the retina detached. In the eight month of life she underwent another ophthalmic surgery abroad, but this also brought no success as far as her vision is concerned and only confirmed, that there is no other option of treatment. Currently, the eyeballs are

almost completely atrophied, but the patient’s mother did not decide on the option of prosthesis. This is important from the perspective of the patient’s appearance, as the lack of fully developed eyeballs is noticeable. The issue is currently the subject of therapeutic and psychological considerations.

According to the mother, the patient developed properly until the age of 2 years and six months when the first signs of autism appeared. The mother observed – as she recollects – rapid regression in verbal and motor functions. The mother claims that up to 2.5 years the patient normally walked, learned to speak, had no difficulties with training of cleanliness, suddenly the development stopped and regression took place. The girl began to be aggressive, she rejected physical contact, was screaming and shouting. She was referred to psychiatrist, who confirmed the ASD diagnosis.

In May 1999, at the age of three, the patient was diagnosed with T1DM, with the onset glucose level 908 mg/dl. The patient was hospitalized on pediatric ward for a month.

In the first years of the patient’s life, there were also other unfavorable phenomena that could affect her emotional development. During the first three years of life the patient and her mother experienced emotional and physical violence from the father who withdraw from the parental role. He abused alcohol and humiliated both of the women. The mother separated with the husband in 2007 and became the only caregiver of the patient, also in terms of finances. The father died in 2018, in the meantime he had no contact with the daughter. The patient has one older sister (42 years old) from the first marriage of the mother, but she has been living in Norway since many years. The source of income for the patient was her social pension and the money the mother earned in casual work, which made their financial situation difficult.

For eight years, beginning from the 7<sup>th</sup> year of age, the patient had behavioral therapy in which she underwent speech training, learned emotions control, aggression management, basic elements of Braille alphabet. The mother regrets that the therapy was not started earlier, as she thinks her daughter would progress even more, however she did not know before about such possibility of treatment.

The patient has good long term memory, she is able to remember dates, names, long texts and recollect them even after many years. However, there is significant discrepancy between academic ability and social intelligence. She has impairment in non-verbal communication, provides excessive information on topics of own interest (music), she is unable to adapt style of communication to social situations, she takes things literally and fails to understand sarcasm or metaphor. The patient has difficulties in initiating and sustaining social relationships, and finds it very difficult to adapt to new situations.

She is very sensitive to sounds and like singing, but because of her vision impairment she cannot develop other artistic abilities, which could be beneficial in her therapy. Very helpful in her development is Community Self Help House leaded by St. Brother Albert Foundation, where she has adequate assistance in her ASD social difficulties, vision impairment and diabetes control. In the community, she tries to perform basic everyday activities. She also likes listen to audiobooks.

At home she is very well organized. All her clothes are sorted in a regular order so that she can find whatever she needs, the same about her cosmetics and other everyday equipment.

Formally she gained gymnasium level of education, however she has no occupational skills that could make her in any way financially independent. The patient is very much attached to her mother, who is in charge of her health and life functioning. On the one hand this is very helpful and important, but it may have also cause some separation problems. The patient has very few relations, even her sister is not present in her life on a regular basis – she visits her only every few months. Also, the strong symbiotic connection to her mother may impair her individuation process. The patient had never had any other close relationship, neither with a friend, nor an intimate one. Obviously, difficulties in this sphere are the consequences of autism itself, but we may speculate that not only. The mother is always present when there is any new contact, prefers to speak instead of the daughter, controlling every interaction. This may be understood as a way of protecting the daughter and manifestation of fear that again something bad could happened to her. On the

other hand, the mother, being the only caregiver, experiences depressiveness, panic attacks and psychosomatic symptoms. She claims they are a sign of long-term overload.

The great engagement of the mother into the patient's life evokes respect and deserves admiration, but this also, in the countertransference, makes it difficult to confront her with some level of over control or overprotection. In general, the mother is well organized, open for support and accepted her life role as a caregiver.

The patient lacks stable male figure. The father was in the family system an aggressor while there was no other positive man, with whom the patient could identify. Also, the patient does not mention any relations with partners or sexual experiences, her sexual orientation was also not declared by her.

The patient is very enthusiastic about her everyday contact with the community workers. She is very positive person, and her good memory, typically described in autistic persons, makes her being well recognized by others. On the level of social functioning, some difficulties may be caused by lack of eyeballs prosthetics. For unknown reasons, they were not implemented so far – this is now being considered.

Nevertheless, the general functioning of the patient and her mother is very good. The patient is adjusted to her daily routine, she is very positive, optimistic and cooperative with her mother. When asked about how she feel about her diseases, she replies that blindness is her greater sadness, although she accepted it. She has no imagination of how the world looks like. In diabetes she does not like the ritual of blood glucose level control and insulin pump administration. Autism is experienced by her as part of whom she is. It is very egosyntonic, she does not treat it as a problem. She claims to be very happy in general.

Although the impact of the mother on the diabetes control of her daughter is high, we do not see the patient as completely dependent. She is trying to be active in the community center, where she is involved in various activities. There her independent effort can be observed.

Currently the patient is being treated with personal insulin pump Medtronic Paradigm 722. Her last available pump download showed daily insulin dose of about 1 IU/kg (65 I.U), 25% de-

livered as a bolus and 75 % as basal insulin infusion. The option of bolus calculator is being used on regular basis and utilized either by patients' mother or Community Self Help House staff. This is an important option, especially in the case of this particular patient, since based on pre-meal blood glucose level and amount of carbohydrates planned to be consumed, the device suggests prandial insulin dose (or correction dose in case of hyperglycemia). Patient's daily carbohydrate consumption, based on pump records is equal to approx. 300 g/day. The change of infusion sets is regular (every 3 days). Due to the lack of reimbursement she is not currently using any CGM (continuous glucose monitoring) system, her last available SMBG (self-monitoring blood glucose) data (covering 2 weeks) showed average blood glucose of 137 mg/dL (SD: 61 mg/dL) based on average of 10.9 measurements per day. HbA1c measured approx. 6 months before last assessment was equal to 7.2% (55 mmol/mol). Overall her glucose control, taking into account the presence of concomitant diseases, should be considered as very good.

The patient is free from advanced, late complications of diabetes, no signs of Hashimoto disease or Coeliac disease were detected. Other regularly performed screening lab tests were of no clinical significance

The patient is not allergic. Father of the patient, in addition to alcoholic disease, suffers from albinism, but she has no signs of that disease. Until 10 year of age, the patient had a reduced sensitivity to pain, now shows a certain level of hypersensitivity

## DISCUSSION

The patient clinical condition is an example of the described in literature comorbidity of ASD and T1DM, with the possible impact of preterm birth and the following collapse during ophthalmic surgery at the age of two. Considering the patients' health status and life conditions (comorbidity of T1DM, autism and blindness, abusive, not engaged father, difficult financial situation) very good treatment results as far as T1DM is concerned were achieved: HbA1c ranging from 7.3 to 6.5 during last 3 years, with average of 1-2 episodes of mild hypoglycemia per week

and no episodes of severe hypoglycemia. Also, regardless of many obstacles and life crises, the patient maintains possibly the best in her conditions, psychological well-being.

Analyzing of the patient's therapeutic success can be found in several important coexisting factors: many years of consequent involvement of the mother in the patient's treatment, cooperation of well-trained staff in the community center and in the diabetology clinic, very good cooperation with the diabetologist, the use of a personal insulin pump and the patient's own coping mechanisms.

According to literature, differentiating between autistic-like features related to blindness and "true" autistic features can be very difficult, and demands clinical experience of children with blindness and their typical development, as well as properly adapted assessment tools [29, 30]. Lack of experience of the typical development patterns in children with blindness, can lead to either giving the child an incorrect diagnosis or overlooking possible co-existing ASD. Either way, the child and their family are at risk of not receiving adequate support [31, 32]

Despite numerous limitations, especially at the beginning of her late, and rather late introduction of behavioral therapy, the patient managed to catch up with many developmental steps. She patient remains optimistic, has a positive attitude to the surrounding reality, takes advantage of regular rehabilitation, and relies on her own psychological resources (optimism, good cooperation, openness to new experiences).

Planning adequate T1DM treatment in this unique case turned out to be a challenge Regardless of whether MDI (Multiple Daily Injection) or CSII (Continuous Subcutaneous Insulin Infusion) would be used, the patient is unable to self-dose insulin. The pump, however, allows for a retrospective precise evaluation of the treatment and therefore this form of therapy was chosen. What seems to be crucial in their functioning is the cooperation with diabetologist and psychiatrist.

In the authors opinion, the key issues that resulted in such a good diabetes control were as follows:

- The usage of personal insulin pump [33-35], that allows to:

- Set the basal infusion rate according to individual insulin requirement – in this case, optimizing nighttime rate of basal insulin infusion was crucial for patient's the feeling of safety;
- Calculate the meal insulin doze based on Bolus Calculator – this option makes mealtime insulin delivery much easier not only for the mother, but also for the staff taking care of the patient
- Retrospective data analysis: based on pump records, the doctor can analyze day by day insulin dosing, including meal and correction boluses, insulin delivery suspends and others.
- The stable and friendly environment in which the patients feels comfortable, patient's behavior is predictable at most cases what, for instance allows pre meal insulin bolusin (vs post meal insulin blousing, which is much less effective metabolically, but sometimes this approach has to be used when the cooperation with the patient is poor and one can not expect how much the patient is going to eat) [36].
- The balanced diet – quantitative and qualitative repeatability of meals on the one hand, and on the other hand the ability to flexibly adapt to the current nutritional needs of the patient, for whom eating is one of the most important areas of experiencing sensory pleasure

What should also be discussed, on a one hand the routine of everyday activities may be helpful in maintaining the stable glucose levels, but on the other hand, because of her autism, the patients sometimes experience strong emotions which are difficult for her to be metalized. Thus, they do influence the stability and require from her proper reactions. She has learned through her behavioral therapy how to calm down, how to deal with anger or anxiety, and through this also how to manage the possible impact of the emotions on her glycaemia. In the case of emotions-related hyperglycemia, the usage of properly set Bolus Calculator to deliver the correction insulin dose is essential.

We also wanted to stress and present the necessity of good cooperation of various parts taking part in her treatment and everyday functioning – the neurologist, psychiatrist, diabetologist,

occupational therapists and nurses in the community, also dieticians who decide about her diet.

Considering possible improvements of T1DM treatments, a good solution for the patient would be the use of real-time continuous glucose self-monitoring with the transmission of the results to the mother, but the mother is not technically able to handle CGM. An additional problem is the lack of a refund possibility for CGM in Poland.

An optimal solution would be a closed insulin loop, but the currently available devices, despite their great technical advancement, still require self-service (the need to count carbohydrates, calibrate sensors), which is beyond the patient's capabilities

The presented case can be a source of knowledge and inspiration, presenting challenges and possibilities in the treatment of people with T1DM and with similar comorbidities. From the therapeutic point of view, it indicates that well planned, individualized therapy may be the basis for creating optimal conditions for the development and improvement of the quality of life of patients with autism, type 1 diabetes and blindness – or other comorbid conditions.

## COMPLIANCE WITH ETHICAL STANDARDS

- Ethical approval for the study was granted by the Jagiellonian University Bioethics Committee no 1072.6120.307.2020.
- The patients provided informed consent to participate in the study.
  - All other authors declare no conflict of interest

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