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# Severe neurological complications in an infant during vitamin $B_{12}$ deficiency treatment: a case report

Alicja Leśniak[A] ✉, Michał Patalan[B], Magdalena Sieńko[C], Iwona Stecewicz[D], Mieczysław Walczak[E], Maria Giżewska[F]

Pomeranian Medical University in Szczecin, Department of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology of the Developmental Age at Independent Public Hospital, Unii Lubelskiej 1, 71-252 Szczecin, Poland

[A] ORCID: 0000-0002-0760-5120; [B] ORCID: 0000-0002-5981-6456; [C] ORCID: 0000-0002-2971-8038; [D] ORCID: 0000-0002-6491-6785; [E] ORCID: 0000-0003-1664-8525; [F] ORCID: 0000-0001-8433-0864

✉ alicjalesniak60@gmail.com

**ABSTRACT**

Disorders of vitamin $B_{12}$ (cobalamin) metabolism in children can be manifested by numerous symptoms. They result from the dysfunction of many systems, including the central nervous system. The most common cause of cobalamin deficiency in infants is inadequate supplementation of the vitamin with food. This mainly affects children who are exclusively breastfed by mothers who follow a diet with insufficient supplementation of vitamin $B_{12}$, including an imbalanced vegetarian or vegan diet. Adequate vitamin $B_{12}$ supplementation is essential for the proper growth and development of a child. However, attempts to compensate for severe vitamin $B_{12}$ deficiency can paradoxically lead to severe adverse reactions to vitamin $B_{12}$ treatment.

In this paper, we present a case of a 10-month-old boy with global developmental delay, muscle hypotonia, and profound vitamin $B_{12}$ deficiency with megaloblastic anemia. The boy developed pathological neurological signs after intramuscular injections of vitamin $B_{12}$. The symptoms included muscle tremors of the upper extremities, head, tongue, and lips. A broad differential diagnosis including inborn errors of metabolism and other genetic disorders is discussed. We describe treatment that led to the complete resolution of symptoms related to the side effects of the $B_{12}$ therapy. The patient's psychomotor development during over 1 year of clinical follow-up is also analyzed.

**Keywords**: cobalamin deficiency; vitamin $B_{12}$ supplementation; involuntary movements; infant; anemia.

## INTRODUCTION

Vitamin $B_{12}$, also known as cobalamin due to its chemical structure which contains a cobalt-containing ring, is supplied to the body with food and stored mainly in the liver. Many proteins are involved in the metabolism of vitamin $B_{12}$. At the initial stage, which takes place in the acidic environment of the stomach, it combines with transcobalamin I to form a protein complex. Then, with the involvement of pancreatic proteases, vitamin $B_{12}$ is separated from transcobalamin I and combines with intrinsic factor (IF) produced by gastric parietal cells. Absorption of this complex takes place in the terminal ileum by binding to a special cubilin receptor. In the enterocyte, vitamin $B_{12}$ is dissociated from the IF and subsequently combined with transcobalamin II to form the active form of vitamin $B_{12}$ called holotranscobalamin. Holotranscobalamin is internalized through a specific receptor and proceeds to further intracellular transformations involving the conversion of vitamin $B_{12}$ to its active cofactors such as adenosylcobalamin, methylcobalamin, or other complementation groups. Vitamin $B_{12}$ metabolism is shown in Figure 1 [1].

Food rich in vitamin $B_{12}$ includes ruminant meat, poultry, fish, shellfish, dairy products, and eggs [2]. Insufficient coverage of daily requirement for vitamin $B_{12}$ leads to abnormal growth and development. The daily requirement for vitamin $B_{12}$ in children is age-dependent. Individual values are shown in Table 1 [3, 4].

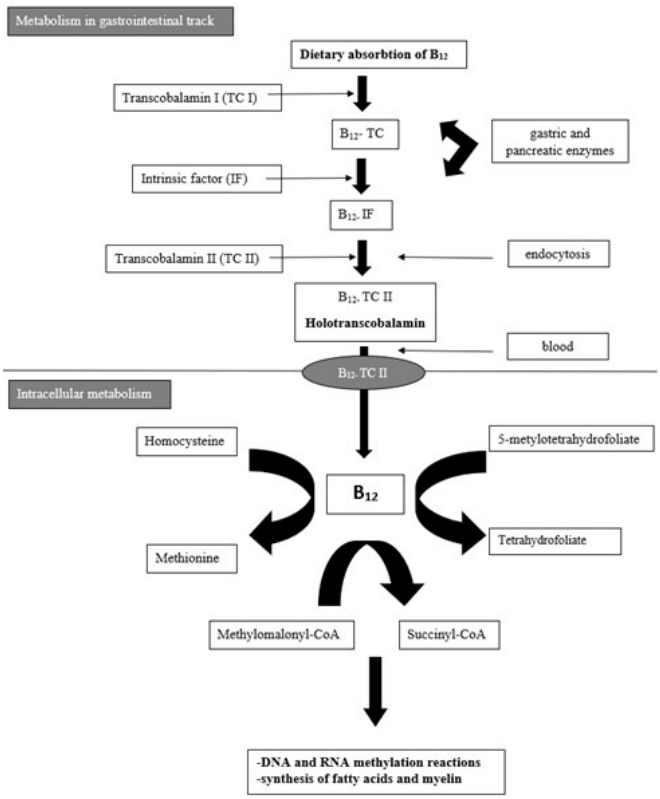


**FIGURE 1.** Vitamin $B_{12}$ (cobalamin) metabolism according to Blau et al. [1] in own modification

**TABLE 1. Dietary reference intakes of vitamin $B_{12}$ in different age groups according to Bernstein et al. [3]**

| Age | Dietary reference intakes of vitamin $B_{12}$ (µg/day) |
|---|---|
| **0–6 months** | 0.4 |
| **7–12 months** | 0.5 |
| **1–3 years** | 0.9 |
| **4–8 years** | 1.2 |
| **9–13 years** | 1.8 |
| **14–18 years** | 2.4 |

Vitamin $B_{12}$ deficiency in newborns, infants, and children is defined based on age-specific values: 0–6 months below 120 pmol/L, 6–12 months below 165 pmol/L, and 12–24 months below 183 pmol/L [5].

Disorders of vitamin $B_{12}$ metabolism in children can be manifested by a number of symptoms. They result from the dysfunction of many systems including the central nervous system (CNS) [6]. Main symptoms of vitamin $B_{12}$ deficiency are shown in Table 2.

**TABLE 2. Symptoms of vitamin $B_{12}$ deficiency based on Dror and Allen [7] in own modification**

| Symptoms of vitamin $B_{12}$ deficiency | |
|---|---|
| **Nervous system** | decreased concentration and attention, apathy, sleep disturbances, decreased muscle tone, delayed psychomotor development, tremors, convulsions, irritability, paresthesias, numbness in the extremities |
| **Gastrointestinal tract** | growth retardation, appetite disorder, loss of taste, burning tongue, trophic lesions of the mucosa, nausea, and vomiting |
| **Blood** | megaloblastic anemia |
| **Other** | skin pigmentation disorders |

In addition to the clinical symptoms described above, there are other characteristics of vitamin $B_{12}$ deficiency, including megaloblastic anemia, typically with increased medium red blood cell volume (MCV), anisocytosis, presence of oval macrocytes, and hypersegmentation of granulocyte nuclei in the peripheral blood smear. In CNS, vitamin $B_{12}$ deficiency is evidenced by pathological changes found on magnetic resonance imaging (MRI) such as the widening of intracerebral spaces, delayed myelination, or frontotemporal atrophy [6, 7]. Treatment of vitamin $B_{12}$ deficiency consists of oral or parenteral supplementation.

The purpose of this case report is to present both vitamin $B_{12}$ deficiency disorder and pathological neurological symptoms in the form of muscle tremors or other involuntary movements observed during the treatment of vitamin $B_{12}$ deficiency. Prophylaxis of vitamin $B_{12}$ deficiency in different age groups is discussed and treatment for profound deficiency of this vitamin is proposed according to the available literature. This treatment helps minimize the risk of side effects from the CNS as described above.

## CASE REPORT

A 10-month-old boy with pathological neurological symptoms was transferred for diagnosis to the Department of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology of the Developmental Age at the Independent Public Hospital of the Pomeranian Medical University in Szczecin, Poland. The symptoms included muscle tremors of the upper limbs, head, tongue, and lips as well as delayed psychomotor development and decreased muscle tone.

The boy was a child of young unrelated parents with negative family history, from second pregnancy and second delivery, born at term, with proper weight (3040 g) and head circumference (33 cm), in good general condition, rated 9/10/10 points according to the Apgar scale. From the beginning of pregnancy, the mother remained on a vegetarian diet and iron supplementation due to anemia (no exact data on the type and degree of her anemia is available). The perinatal period was uncomplicated. When the boy was 3 months old, decreased muscle tone was observed. Consequently, the child was subjected to physiotherapy using the Vojta method, which resulted in a slight improvement. Around the age of 6 months, a decrease in appetite was observed. At 9 months of age, due to delayed psychomotor development and decreased muscle tone, the boy was hospitalized at the department of neurology. The patient was unable to sit, pull himself up to sit, or crawl. He could not hold his head in a stable position when lying on his stomach. In laboratory investigation, the blood count revealed megaloblastic anemia. Metabolic analysis showed decreased $B_{12}$ concentration, abnormal tandem mass spectrometry (MS/MS) results (reduced amino acid concentration of methionine and free carnitine), as well as significantly elevated methylmalonic acid (MMA) concentration in urinary organic acid profile. Detailed laboratory results are shown in Table 3.

**TABLE 3. Patient's laboratory results on admission to the department of neurology**

| Laboratory results | | |
|---|---|---|
| **test** | **result** | **norm** |
| **CBC: Hb (g/dL)** | 7.6 | 9–14.6 |
| **Ht (%)** | 21.3 | 36–51 |
| **RBC (mln/µL)** | 2.10 | 3.90–5.00 |
| **MCV (fl)** | 101.40 | 80–96 |
| **MCH (pg)** | 36.20 | 25–26 |
| **MCHC (g/dL)** | 35.70 | 32–36 |
| **WBC (ths/µL)** | 7.70 | 5–19.5 |
| **PLT (ths/µL)** | 207 | 200–550 |
| **$B_{12}$ concentration (pg/mL)** | 50 | 191–663 |
| **MS/MS (µmol/L)** | methionine 6.46<br>free carnitine 6.07<br>total carnitine 16.37 | 8–59<br>7.4–84<br>24–188 |
| **GCMS (mmol/mmol creatinine)** | methylmalonic acid 1020 | <20 |

CBC – complete blood count; Hb – hemoglobin; Ht – hematocrit; RBC – red blood cell; MCV – medium cell volume; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; WBC – white blood cell; PLT – platelets; MS/MS – tandem mass spectrometry from dried blood spot; GCMS – gas chromatography – mass spectrometry from urine

Due to the slightly widened cerebral ventricles on brain ultrasound, an MRI scan of the boy's head was performed. The scan revealed dilatation of the parieto-cerebral spaces with wide Sylvian furrows, widened ventricular system and frontal horns of the lateral ventricles. Extracerebral and intracerebral fluid spaces dilatation suggested brain atrophic. Encephalopathic electroencephalography (EEG) showed abnormal basal activity while a video-EEG study did not record any seizure-like incidents.

Treatment included supplementation of 1 unit of red blood cell concentrate and 2 doses of vitamin $B_{12}$, 100 µg each, administered by intramuscular injection on 2 consecutive days. On the day the boy received the second dose of vitamin $B_{12}$, he was discharged home. Later that day, the child demonstrated tremors in his upper limbs, head, tongue, and mouth. For this reason, the mother and the child reported to the emergency room of the nearest hospital. At that time, laboratory tests showed significantly elevated serum vitamin $B_{12}$ levels (5570 pg/mL), hyper-transaminasemia (alanine transferase 265.93 U/I N 7–40, AST 179.27 U/I N 20–72), and elevated lactate dehydrogenase (LDH 1595.29 U/I N 120–300). Anticonvulsant treatment (diazepam, clonazepam, chlorpromazine and midazolam) was administered. As the treatment brought no clinical improvement, the boy was transferred back to the department of neurology. Elevated vitamin $B_{12}$ levels (1332 pg/mL), elevated LDH levels (788 U/L) and hyper-transaminasemia were confirmed by laboratory investigation. A suspicion of an inborn error of metabolism was raised and the boy was transferred for further diagnosis to the Department of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology of the Developmental Age. On admission, the child's general condition was assessed as good, yet apparent muscle tremors in the upper limbs, head, tongue, and lips continued and his psychomotor development was delayed. The boy kept his hands closed, he could not support himself on the forearms and was not able to hold his head lifted. He presented reduced muscle tone in the head-to-toe axis. In anthropometric measurements, his head circumference was 43.5 cm (3–10c), weight 7.4 kg (3c), length 75 cm (3c). The boy continued to be breastfed but during severe tremors he had to fed via gastric tube. In laboratory tests, blood count showed increased MCV 91.7 fl (N 70–82), slightly elevated LDH 364 U/I (N 120–300), elevated vitamin $B_{12}$ concentration 720 pg/mL (N 191–663) with a tendency to decrease but remaining in the upper limit of $B_{12}$ normal values (581 pg/mL). Folic acid concentration and iron metabolism were within the normal range while homocysteine was elevated up to 25.6 µmol/L (N < 8 µmol/L). In metabolic investigation, the result of MS/MS was normal and the urine organic acid profile showed no elevated MMA concentration (19.1 µmol/mmol creatinine with N < 25 µmol/mmol creatinine). Since the child demonstrated symptoms of extrapyramidal disorders, as part of the differential diagnosis to exclude tetrahydrobiopterin metabolic disorders, urinary pterin profile and dihydropterin reductase activity were checked and proved to be normal. On imaging studies, electroencephalography recordings were within normal range and no seizures were observed clinically. The mother's vitamin $B_{12}$ concentration was normal but from the sixth month of the child's life she was treated with vitamin $B_{12}$ supplements.

Taking into account the laboratory and clinical findings described above, the suspicion of tremors caused by vitamin $B_{12}$ supplementation in a state of severe deficiency was raised. Treatment with clonazepam was introduced, achieving a target dose of 0.1 mg/kg/day. From the fifth day of full-dose therapy, a reduction in tremors was observed. On the nineth day of full-dose treatment, only minimal tremors of the tongue, head, and upper extremities were still observed. Therapy with clonazepam at a dose of 0.1 mg/kg/day was maintained for the following days. Next, the dose was gradually reduced until complete withdrawal. Due to persistent appetite disorders and unsatisfactory weight gain, the boy was consulted by a neurologopedist and a dietician. Therapy aimed at improving articulatory and swallowing organs was applied and resulted in some improvement. Two months after the introduction of the treatment, the complete disappearance of muscle tremors was observed. Despite the general developmental physiotherapy and normalization of serum vitamin $B_{12}$ levels, delayed psychomotor development and significantly reduced muscle tone were still detected. To further diagnose the neurodevelopmental disorders which could not be explained solely by vitamin $B_{12}$ deficiency, whole exome sequencing (WES, Centogene, Rostock) was performed. Molecular investigation detected a change in the *SLC9A7* gene, variant: c.203G>A(p.Arg68Gln). It is a missense mutation, a variant of unknown clinical significance (VUS) located on the X chromosome. Due to the mode of sex chromosomes inheritance, the boy's mother was also tested for the presence of the above mutation and was confirmed to be an asymptomatic carrier.

During the 12-month follow-up, the boy was checked several times at our department. No significant abnormalities were observed in laboratory studies and tests evaluating his metabolic status. The patient's development improved significantly. Currently, the 22-month-old boy is gaining weight properly, sits up independently, crawls, walks supported by his hand, shows interest in toys, and pronounces single words. He continues to be under the care of our center and is receiving intensive somatosensory physiotherapy.

## DISCUSSION

Neurological abnormalities as a paradoxical response to supplementation of profound vitamin $B_{12}$ deficiency have already been described several times in the literature. The paper by Ozer et al. presents 2 girls aged 11 months and 12 months with vitamin $B_{12}$ deficiency whose mothers were also deficient in this vitamin. The children were exclusively breastfed. They had a reaction similar to our patient – tremors of the head, tongue, throat, and lower limbs after supplementation of vitamin $B_{12}$ at a dose of 100 µg/day intramuscularly on the second and third day, respectively. After a 6-day treatment with clonazepam at a dose of 0.1 mg/kg/day, improvement was achieved with the

complete resolution of symptoms on the fifteenth day in the first girl and on the twenty first day in the second child [8].

In 2013 Patiroglu et al. described a 9-month-old boy with severe vitamin $B_{12}$ deficiency, born to a mother deficient in vitamin $B_{12}$, who also presented with similar head and tongue tremors and involuntary movements 3 days after intramuscular supplementation of vitamin $B_{12}$ at a dose of 100 µg/day. In his treatment clonazepam at a dose of 0.1 mg/kg/day was introduced achieving complete resolution of symptoms after 15 days [9]. In the same year of 2013, Carman et al. described a 13-month-old girl and a 16-month-old boy treated with vitamin $B_{12}$ at a dose of 1000 µg/day, who developed upper limb tremors after a 3-day and a 5-day vitamin $B_{12}$ supplementation, respectively. The symptoms resolved completely on the sixth and third day after the treatment with clonazepam at a dose of 0.1 mg/kg/day was initiated [10].

In addition to the cases discussed above, other descriptions of paradoxical reactions to vitamin $B_{12}$ supplementation can be found. They mainly include tremors in the upper and lower limbs, head, tongue and mouth. These symptoms are most commonly found in infants with profound vitamin $B_{12}$ deficiency (<80 pg/mL) between 6–20 months of age. Most vulnerable are the children exclusively breastfed whose mothers were found to be vitamin $B_{12}$ deficient during pregnancy. According to Dror and Allen in healthy infants born to mothers with normal vitamin $B_{12}$ levels, there is about 25–30 µg vitamin $B_{12}$ stored in the liver, while in infants born to mothers with vitamin $B_{12}$ deficiency, it amounts only to 2–5 µg [11]. Symptoms of vitamin $B_{12}$ deficiency in infants usually appear between 4–10 months of age.

In the literature, there is ambiguous data regarding vitamin $B_{12}$ supplementation. In October 2022, Recommendations of the Joint Committee of Pediatric Hematology-Oncology Chapter and Pediatric and Adolescent Nutrition Society of the Indian Academy of Pediatrics were published. Proposed doses of vitamin $B_{12}$ supplementation in oral and parenteral therapy in $B_{12}$ deficiency disorder are shown in Tables 4 and 5 [12].

**TABLE 4. Oral treatment of vitamin $B_{12}$ in infants and children based on Chandra et al. [12] in our modification**

| Days of treatment | Infants | Children |
|---|---|---|
| **1–7 day First week** | 500 µg 1x/day | 1000 µg 1x/day |
| **8–14 day Second week** | 500 µg every other day | 1000 µg every other day |
| **15–21 day Third week** | 500 µg twice per week | 1000 µg twice per week |
| **22–28 day Fourth week** | 500 µg once per week | 1000 µg once per week |
| **5–8 week Next month** | 500 µg twice a month | 1000 µg twice a month |
| **Next 3-months** | 500 µg once a month | 1000 µg once a month |

**TABLE 5. Parenteral treatment of vitamin $B_{12}$ in infants and children based on Chandra et al. [12] in our modification**

| Parenteral vitamin $B_{12}$ treatment given by intramuscular IM (or deep subcutaneous SC or intravenous IV) route | | |
|---|---|---|
| **days of treatment** | **infants** | **children** |
| **1–3 day** | 25 µg 1x/day | 25 µg 1x/day |
| **4–10 day or 4–21 day (in patients with neurological features)** | 50 µg 1x/day | 100 µg 1x/day |
| **11–18 day or 22–29 day (in patients with neurological features)** | 100 µg every other day | 100 µg every other day |
| **Next 4-weeks** | 1000 µg once a week | 1000 µg once a week |

In 2019, Baroni et al. proposed doses of oral vitamin $B_{12}$ supplementation based on the following supplementation scheme. It is based on the actual serum levels of $B_{12}$ in order to guarantee a daily amount of absorbed $B_{12}$ corresponding to 5-fold of the Recommended Dietary Allowance for $B_{12}$ (Tab. 6) [13].

Muscle tremors may be a symptom of vitamin $B_{12}$ deficiency but they can also occur as a complication of treatment. In a state

**TABLE 6. Proposed oral supplementation scheme for vitamin $B_{12}$ deficiency by Baroni et al. [13]**

| | Serum $B_{12}$ <75 pmol/L | Serum $B_{12}$ between 75–150 pmol/L | Serum $B_{12}$ between 150–220 pmol/L | Serum $B_{12}$ between 220–300 pmol/L |
|---|---|---|---|---|
| **Pregnant and lactating women** | 1000 µg/day for 4 months | 1000 µg/day for 3 months | 1000 µg/day for 2 months | 1000 µg/day for 1 month |
| **Children aged 6 months to 3 years** | a daily single dose of 250 µg or 3 daily doses of 10 µg for 4 months | a daily single dose of 250 µg or 3 daily doses of 10 µg for 3 months | a daily single dose of 250 µg or 3 daily doses of 10 µg for 2 months | a daily single dose of 250 µg or 3 daily doses of 10 µg for 1 month |
| **Children aged 4–6 years** | 500 µg 4 times/week for 4 months | 500 µg 4 times/week for 3 months | 500 µg 4 times/week for 2 months | 500 µg 4 times/week for 1 month |
| **Children aged 7–10 years** | 500 µg 6 times/week for 4 months | 500 µg 6 times/week for 3 months | 500 µg 6 times/week for 2 months | 500 µg 6 times/week for 1 month |
| **11 years and above** | 1000 µg/day for 4 months | 1000 µg/day for 3 months | 1000 µg/day for 2 months | 1000 µg/day for 1 month |

of severe cobalamin deficiency tremors are most frequently observed between the third and fifth day after parenteral administration of a high dose of vitamin $B_{12}$ [14].

Pathogenic variant in the *SLC9A7* gene detected in our patient by WES can cause intellectual disability type 108 (OMIM #301024 X-Linked Intellectual Developmental Disorder-108). It is characterized by psychomotor and intellectual developmental delay, hypotonia, and discrete dysmorphic features. The inheritance of the mutation in the *SLC9A7* gene is X-linked recessive. This means that mainly boys are affected while girls are only asymptomatic carriers (to date, no symptoms in girls who are carriers of pathologic variant in this gene have been described) [15]. Based on the information obtained from The Human Gene Mutation Database (HGMD), ClinVar, and CentoMD®, it can be assumed that the detected variant in the *SLC9A7* gene is probably pathogenic and may be related to the clinical symptoms observed in our patient. The way to confirm the pathogenicity of this variant is to further observe and assess the boy's psychomotor development in the near future.

## CONCLUSIONS

Based on the patients described in the literature who developed tremors during vitamin $B_{12}$ deficiency treatment, it can be noted that the first dose of vitamin $B_{12}$ that most of them received was in the range of 100–1000 µg/day. Recent recommendations for vitamin $B_{12}$ treatment emphasize that in children with profound vitamin $B_{12}$ deficiency, treatment should be initiated with lower doses of 25–50 µg/day. Lower vitamin $B_{12}$ doses should reduce the risk of nervous system complications and minimize the risk of secondary hypokalemia. Supplementation of severe vitamin $B_{12}$ deficiency with excessive doses of vitamin $B_{12}$ may result in intensive stimulation of the biochemical metabolism of vitamin $B_{12}$ and folic acid as well as a transient imbalance of metabolic pathways. In the course of deep vitamin $B_{12}$ deficiency treatment, transient hyperglycemia occurs resulting in the inhibition of spinal cord and brainstem function. Moreover, NMDA receptor-mediated stimulation of the cerebral cortex may take place and this can lead to the occurrence of tremors and lowering of the threshold for seizure excitability [14].

Prevention of severe vitamin $B_{12}$ deficiency in infants plays a key role in maintaining homeostasis and should be introduced as early as in fetal life. It consists of adequate vitamin $B_{12}$ supplementation in mothers at risk (low social status, deficient or inadequately balanced diets, diseases with vitamin $B_{12}$ malabsorption, history of megaloblastic anemia, etc.).

Despite advanced laboratory investigation that included metabolic status evaluation and many specialized imaging tests, the genetic background of observed symptoms should be always kept in mind. Although WES is still not readily available in Poland, this case report shows that WES may broaden our view of a patient beyond the organic causes of observed abnormalities.

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