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Case Report: Dyskeratosis Congenita in Two Filipino Siblings

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Abstract

Dyskeratosis congenita (DC) is a rare inherited multi-system disease. The classic triad of DC involves reticulated hyperpigmentation, nail dystrophy, and oral leukoplakia. We report two Filipino siblings with clinical features of DC and genetic test results. The proband presented with reticular skin hyperpigmentation and nail dystrophy at age six, and his sibling presented with similar cutaneous findings around the same time. At age nine, the proband developed tongue leukoplakia. He was admitted to our hospital for a 4-day history of gum and tongue bleeding, as well as fever. The patient was diagnosed with DC and work-up was done. Work-up for sepsis was normal. Lymphocyte subset enumeration revealed reduced levels of B cells and NK cells. Serum immunoglobulins were all normal. Genetic testing revealed a DKC1 mutation for both siblings. These two cases illustrate how despite having a similar genetic mutation, there can be a variable manifestation of the disease. Early diagnosis, work-up, and holistic management would be important in managing rare diseases like this that affect multiple organ systems.

Keywords: Dyskeratosis Congenita, Zinsser-Engman-Cole Syndrome, Primary immunodeficiency, Bone marrow failure

INTRODUCTION

Dyskeratosis congenita (DC) is a rare inherited bone marrow failure (BMF) disease. It is also known as the Zinsser-Engman-Cole syndrome, first described by Zinsser in 1906. The classic triad of DC is reticulated hyperpigmentation, nail dystrophy, and oral leukoplakia.(1) Aside from mucocutaneous manifestations, it can present with a range of somatic abnormalities (ophthalmic, dental, skeletal, pulmonary, gastrointestinal, and neurologic) .(2) DC has also been associated with BMF, increased predisposition to malignancy, fatal pulmonary complications, and immunodeficiency.(2,3) These would be the most common causes of early deaths in patients with DC.

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Studies have identified three patterns of inheritance for DC: X-linked recessive, autosomal dominant, or autosomal recessive.(2) Genetic studies have identified ten genes involved in DC.(4) Mutations in these genes affect the telomerase complex causing defective telomere maintenance which leads to early cell senescence and apoptosis which explains BMF in these cases. Despite advances in genetic studies, in 30-40% of cases, a genetic basis remains undetectable.(5)

Here, we describe two Filipino siblings with clinical features of DC and genetic test results. To our knowledge, this is the second case report of DC in the Philippines.

CASE REPORT

The proband was born term to non-consanguineous parents. While growing up, the patient was noted to have developmental delay, particularly in gross motor and expressive language. Vaccines were given according to the Philippine immunization schedule without any untoward incident.

At the age of six, he presented with reticular skin hyperpigmentation over the neck, back, and extremities. Similar cutaneous findings were observed in his older sibling around the same time. Both siblings later developed epiphora. They were brought to a local hospital where they were told to have dyskeratosis congenita. A bone marrow aspiration biopsy was done which revealed amegakaryocytic thrombocytopenia, while normal results were seen for his older sibling. They were not advised with any other work-up or treatment. Both had no frequent infections nor hospitalizations. Aside from his sibling, no other family member presented with similar findings (Figure 1).

Based on the First NIH workshop in 2008, recommended treatment for BMF in DC patients should be hematopoietic cell transplant (HCT).(5) HCT is the only definitive treatment for BMF, however it will not address the underlying pathology. From a recent study by Gadalla and colleagues, there was significant improvement in the 5-year overall survival probability of DC patients who underwent HCT in recent years (2000-2009) compared to previous years.(6) Use of reduced intensity conditioning and transplantation from HLA-identical siblings are among several factors associated with improved overall survival mentioned in this study and in other reports.(6-9)

However, HCT in the Philippine setting is costly and impractical, lacking both in expertise and experience in doing HCT for immunodeficiency cases. In cases where HCT cannot be done, androgen therapy is recommended.(5) Currently, only a few studies on the efficacy of androgen therapy in patients with DC have been reported.(10,11) In asymptomatic patients, monitoring and disease surveillance will suffice.

A few studies have evaluated the immunologic profile of patients with DC. In a study by Jyonouchi and colleagues, they observed a clinical spectrum of immune-deficiency ranging from common variable immunodeficiency (CVID) to T+B-NK- severe combined immunodeficiency (SCID).(12) Similar to the most common pattern of immunodeficiency found in their study, our patient exhibited reduced levels of B cells and NK cells. Normal levels of immunoglobulins in our patient could possibly explain the absence of recurrent infections.

Only one other case of DC has been reported in the Philippines. Bas-Bucao and colleagues reported a patient who presented with the classic triad of DC, BMF and recurrent infections.(13) Their patient presented with similar genetic mutation as in our patients. DKC1 gene mutation is the most common genetic mutation in patients with DC and accounts for 30% of cases(1,4) DKC1 mutations are also known to have a wide variety of manifestations, some presenting with the classical course of DC, while others can present with the severe phenotype described as Hoyeraal -Hreidarsson (HH) syndrome – presenting with pancytopenia, intrauterine growth delay, developmental delay, immune deficiency, and cerebellar hypoplasia.(14,15) On the other hand, DKC1 mutation can also be present in asymptomatic patients or carriers.

CONCLUSION

Dyskeratosis congenita is a rare, inherited multi-system disease. These two cases illustrate how despite having a similar genetic mutation, there can be a variable manifestation of the disease. Finally, to better care for these patients, early diagnosis, work-up, and holistic management would be important in managing rare diseases that affect multiple organ systems.

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Case Report: Congenital Insensitivity to Pain and Anhydrosis in a Boy Presenting with Chronic Osteomyelitis

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Abstract

Hereditary sensory and autonomic neuropathy type 4, also known as congenital insensitivity to pain and anhydrosis (CIPA), is a rare disorder characterized by a defect in the ability to feel pain and detect temperature, and the inability to sweat, with some form of intellectual disability. This condition is caused by a mutation in the human TrkA (NTRK1) gene and can be diagnosed clinically and through definitive laboratory tests, including genetic testing.

A 6-year-old male consulted for a painless, non-healing wound on his right big toe. He had several unrecalled injuries and recurrent wound infections in the past, with episodes of hyperthermia and the absence of sweating. He had a history of self-mutilating behavior such as finger biting and wound manipulation, as well as the presence of developmental delay. He was referred to various subspecialties for evaluation and co-management. He was given antibiotics and eventually underwent wound debridement and curettage. His parents were advised on injury prevention, daily evaluation for possible unrecognized wounds, and temperature monitoring. He was also referred to rehabilitation medicine for intervention of his developmental delay.

There is no specific treatment for CIPA. Diagnosis is essential to help prevent associated complications and adequately manage specific problems for better quality of life.

Keywords: congenital insensitivity to pain and anhydrosis, CIPA, hereditary sensory and autonomic neuropathy, HSAN type 4

INTRODUCTION

Hereditary sensory and autonomic neuropathy (HSAN) type 4 also known as congenital insensitivity to pain and anhidrosis (CIPA) is a rare disorder characterized by a defect in the ability to feel pain and detect temperature, the inability to sweat, and the presence of some form of intellectual disability. It is transmitted by autosomal recessive inheritance but sporadic cases can occur. The exact pathophysiology of all the symptoms is not yet fully understood. It is linked to a mutation in the human TrkA (NTRK1) gene. This condition can be diagnosed clinically and through laboratory tests, including genetic testing.

CASE REPORT

A 6-year-old boy consulted for a painless, non-healing wound on his right big toe. Two months prior to the consult, his mother noted a puncture wound on the plantar aspect of his right big toe but the boy could not recall how he got his wound. Despite regular cleaning with soap and water, and oral antibiotic treatment, the painless wound continued to ulcerate, eventually losing full skin thickness and exposing his bone. This was associated with recurrent fever. He was then brought to the emergency department for proper management.

At birth, the boy was managed as a case of neonatal sepsis due to an "absence of response" (he did not cry/react to painful stimuli) after he was given an intradermal vaccine (BCG). He was discharged after completion of antibiotics but the condition was not fully worked up. He would continue not to cry during vaccine administration at the local health center where he completed the expanded program for immunization.

While growing up, his parents observed that he was insensitive to or cannot feel high temperatures because he would frequently sustain burns from playing with lit matchsticks or from holding hot cooking pan lids. His uncle once caught him holding a fire and just observing his fingers get burned. They also noticed his inability to feel pain. There was an instance when he continued to peel off the skin of a fruit despite the persistent bleeding of his finger from the knife cut. He has sustained

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Case Report: Epistaxis as a presenting symptom of Rheumatic Aortic Regurgitation

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Absract

Epistaxis is a common complaint in the pediatric emergency room. We report a case of a 14 year old male who presented with epistaxis as a prominent symptom of rheumatic fever with aortic regurgitation. Though an extensive literature search reveal that there have been published case reports of epistaxis in adults with rheumatic mitral stenosis, there has been no published reports of aortic regurgitation presenting as epistaxis in pediatric rheumatic aortic regurgitation. Adequate blood pressure control and nasal packing controlled the patient's nose bleeding. Thus, rheumatic fever shall be a differential for a patient presenting with epistaxis. Prompt diagnosis and evaluation are needed to prevent the complications of untreated rheumatic fever.

Keywords: Epistaxis, rheumatic fever, aortic regurgitation, Jones criteria

INTRODUCTION

Epistaxis or nose bleeding is very common in the pediatric population. In children, usual causes of epistaxis include trauma, drying of the nasal mucosa, hypertension, inherited bleeding disorders, tumors, and thrombocytopenia.(1) The 1944 Jones Criteria included epistaxis as a minor criteria for the diagnosis of acute rheumatic fever (RF). However, the non-specificity of epistaxis as a symptom led to its removal in the succeeding revisions of the Jones criteria.(2) Though an extensive literature search reveal that there have been published case reports of epistaxis in adults with rheumatic mitral stenosis,(3) there have been no published reports of aortic regurgitation (AR) presenting as epistaxis in pediatric rheumatic aortic regurgitation. Here we report a case of a 14 year old male with epistaxis as a presenting symptom of acute rheumatic fever.

CASE REPORT

A 14 year old Filipino male presented with profuse nasal bleeding at the emergency room. The epistaxis began 6 weeks prior to admission which resolved with ice pack application. There were no associated signs and symptoms at this time.

Fever started to appear at 3 weeks prior to admission, which was associated with left knee pain that migrated to the left shoulder. This persisted in the interim until the day of admission, when there was recurrence of epistaxis which was continuous, lasting for more than 10 hours, prompting consult at our institution.

On admission at the emergency room, the patient was hypertensive with a BP of 150/60. A grade 3/6 diastolic murmur was heard at the left upper parasternal border. Chest radiograph was essentially normal. A 12 Lead ECG showed sinus tachycardia with no chamber enlargement. 2D Echocardiography showed mild mitral regurgitation and moderate aortic regurgitation, consistent with rheumatic carditis. The valves were not thickened and no vegetations were noted. Anti- streptolysin O titers were elevated (>400IU/mL) He was given Benzathine Penicillin G 1.2 M units intramuscularly and was started on Aspirin at 60 mg/kg/day. Enalapril (10mg) once a day and Furosemide (40mg/tab) were also started.

On the 2nd hospital day, there was a recurrence of profuse epistaxis. Initial CBC showed anemia with a hemoglobin count of 89g/L, thus, he was transfused with packed RBC. His prothrombin time and aPTT were within normal range. Aspirin was shifted to Prednisone at 2 mg/kg/day. He was referred to the otorhinolaryngology service for further evaluation. Digital compression and anterior

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In Review: Tetanus

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CASE STUDY

A previously healthy 11-year-old boy was transferred from community hospital to a referral center due to generalized stiffness and muscle spasm. The family had no vaccination record available and a vague recollection of possible vaccinations. The child had been in his usual state of good health until approximately 9 days prior to presentation, when he had stepped on a rusty nail while working with his carpenter father. There had been no wound care. One week following this injury, the child experienced pelvic and back pain followed by spasms in the lower extremities, trismus and then generalized muscle spasm. Nine days after his injury, he developed generalized rigidity, with initial lower extremity stiffness spreading to the upper extremities. Taken to a local clinic, the patient received an intramuscular dose of equine tetanus antiserum, metronidazole and diazepam. There was no clinical change with treatment. Given his grave clinical condition, the child was transferred.

Upon admission, the patient was opisthotonic, with hyperextended limbs, generalized spasms every minutes, respiratory distress and trismus. There was no report of autonomic instability.

The patient was placed in an isolated room, with minimal light and noise. He received continuous IV fluids, penicillin 2,775,000 UI q 6 and metrondazole277 mg q 8, diazepam by continuous infusion at approximately 8 mg over 8 hours and ranitidine 37 mg daily. On the third day following transfer, with minimal clinical improvement, a magnesium sulfate infusion of 1 gram/day was started, ranitidine was discontinued and nasogastric feeds of Pediasure begun and advanced. Vitamin B complex was added to the IV fluids. On day 13 following admission, physical therapy was begun, the diazepam and magnesium infusions were discontinued and po bid diazepam was started. Antibiotics were continued for 13 days total. The recovery was complicated by varicella infection diagnosed on the 16th day of hospitalization for which he was treated with valacylovir and paracetamol. The child was discharged home 24 days after admission.

Introduction and Epidemiology

The above scenario plays out frequently in many parts of the world. Regrettably, more than 40 years after being labelled "the inexcusable disease," tetanus still represent a lethal menace in many regions of the world.(1) The World Health Organization (WHO) reported 13,502 cases of this preventable disease in 2016.(2) However, surveillance is believed to be poor and given the inaccessibility of health care to many in the world (conflict zones, etc.), it is likely the actual is incidence is much higher.(3)

Data from 2015, estimated that global mortality from tetanus was 56,743 (95% uncertainty interval 46,473-84,948) of which 19, 937 (95% uncertainty interval 17,021- 23,467) occurred in the neonatal period. Although disturbingly high for a preventable disease, these levels represents a 90 and 81% decrease in deaths from neonatal and non-neonatal tetanus respectively since 1990, when there were an estimated 337,022 deaths.(4) In addition to the suffering, morbidity and mortality caused by tetanus, it is not irrelevant that the direct cost of treatment in resource limited settings (RLS) may be twofold the annual salary of a laborer, not including long-term rehabilitation and opportunity costs.(3)

Spikes in the incidence of tetanus have been reported in post-disaster areas, highlighting the predisposition in an under-vaccinated population.(5-8) There is evidence that young males are disproportionately at risk due to

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Brief Communication: The Diagnostic Accuracy of Recombinant ESAT-6, CFP-10, MTb Rv0222 and MTb38 kDa in the Serological Diagnosis of Pediatric Patients with Infection and Disease

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Abstract

Rationale: Develop a fast and accurate assay for serologic diagnosis of Latent TB Infection (LTBI) and Disease

Objective: Determine the diagnostic accuracy of recombinant ESAT 6, CFP 10, MTb Rv0222 and MTb 38kDa in the serological diagnosis of LTBI and Disease among pediatric patients

Methodology: A cross sectional cohort design was used in this study. Diagnostic tests for LTBI and TB Disease using antibodies against the recombinant antigens were carried out using ELISA in sera from children aged 4 to 18 years who were diagnosed with LTBI, TB Disease and controls. Results were analyzed using the Receiver Operating Characteristics (ROC) curve and Areas Under the Curve (AUC). Sensitivity, specificity, negative and positive predictive values were calculated.

Results: Only ESAT 6 can discriminate LTBI with an AUC of 0.672, specificity of 65.2%, sensitivity of 43.5%, PPV of 53.6% and NPV of 55.6%. *Kappa* coefficient is 0.087 with a *p* value of 0.546. Meanwhile, the antigens CFP 10, MTb Rv 0222 and 38kDa can discriminate TB Disease with AUC values of 0.626, 0.640 and 0.606 respectively. The computed *kappa* for CFP 10 is 0.174 ($p = 0.226$), for MTb Rv 0222 is 0.130 ($p = 0.300$) and for MTb 38kDa is 0.130 ($p = 0.374$). Specificity ranges from 30.4% to 69.6%, sensitivity from 43.5% to 82.6%, PPV from 54.3% to 57.1% and NPV from 56% to 61.1%. However, the results were not statistically significant.

Conclusion: The results demonstrate that the serological assay based on the recombinant antigens did not efficiently distinguish LTBI and TB Disease from controls.

INTRODUCTION

Tuberculosis (TB) continues to be the leading cause of death in the world from a single pathogen. The World Health Organization estimates that 9.27 million new cases of Tuberculosis occurred in 2007 (at the ratio of 139 cases for every 100,000 population) as compared to the 9.24 million new cases (at the ratio of 140 cases for 100,000 population) in 2006.(1) One of the most remarkable feature of this pathogen is its capacity to generate a latent infection. The risk of progression from Latent TB Infection (LTBI) to TB Disease is higher immediately after infection with the bacillus, although it decreases over time. LTBI is characterized by an asymptomatic phase which can persist for many years with the risk of disease progression.(2) The tuberculin skin test (TST) had been used for almost a century to support the diagnosis of active and latent TB infections. The main drawback with its clinical use is its lack of specificity due to cross reactivity with proteins present in other mycobacteria such as *Mycobacterium bovis* Bacillus Calmette-Guerin (BCG) vaccine strain and Mycobacterium avium.(3) Compared to adults, the yield of microbiologic studies in children tends to be lower because children below ten years old have difficulty expectorating, which results in failure to obtain adequate sputum specimen and childhood tuberculosis is paucibacillary.(4) Since bacteriologic diagnosis of TB in children is difficult, clinicians must rely on clinical and radiologic examinations which have low specificity and may produce a high proportion

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Original Article:
Effect of Ursodeoxycholic Acid in Addition to Phototherapy on Neonatal Indirect Hyperbilirubinemia Among Full Term Infants: A Meta-Analysis

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Abstract

Background: Indirect hyperbilirubinemia is a common problem in the postnatal period, conventionally treated with exchange transfusion and phototherapy. Ursodeoxycholic acid (UDCA) combined with phototherapy as treatment for jaundice has been explored to help decrease total serum bilirubin (TSB) levels. A review may be useful to assess its effectiveness.

Objectives: To determine the effect of UDCA with phototherapy in reducing TSB levels in neonatal indirect hyperbilirubinemia.

Search methods: Comprehensive search of MEDLINE, CENTRAL, WHO Network of Collaborating Clinical Trials Register, ClinicalTrials.gov, Google Scholar, HERDIN and Philippine Index Medicus was conducted for trials published until July 2016. Reference lists from eligible studies were also checked for additional articles.

Selection criteria: Randomized and quasi-randomized controlled trials evaluating the effect of UDCA with phototherapy in decreasing TSB levels in neonatal indirect hyperbilirubinemia.

Data collection and analysis: Two authors assessed trial quality and extracted data, and used Review Manager for statistical analysis with fixed- and random-effects models.

Main results: Two trials with a total of 280 participants showed significant decrease in TSB levels given UDCA and phototherapy versus phototherapy alone after 12 hours (MD -2.74 [95% CI -3.10, -2.39], p<0.00001, I^2=38%), 24 hours (MD -3.38 [95% CI -5.24, -1.52], p=0.0004, I^2=88%), and 36-48 hours (MD -1.75 [95% CI -3.42, -0.09], p=0.04, I^2=98%). It also decreased duration of phototherapy (MD -23.30 [95% CI -34.2, -12.33], p<0.00001, I^2=95%).

Authors' conclusions: Results were heterogeneous however may still suggest that UDCA with phototherapy decrease TSB levels and duration of phototherapy in indirect hyperbilirubinemia in neonates.

Keywords: Ursodeoxycholic acid, Term infants, Neonates, Hyperbilirubinemia

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BACKGROUND

Neonatal jaundice is a common problem among full term infants during the immediate postnatal period, usually due to an increase in indirect bilirubin (Bertini, 2001). This occurs because infants have an increased rate of bilirubin production and a decreased rate of bilirubin elimination.(1,2)

Physiologic jaundice is an indirect hyperbilirubinemia that occurs after the first day of life and can last up to 1 week, which can occur in up to 60% of normal newborns. (3,4) Normally, total serum bilirubin (TSB) concentrations peak in the first 3 to 5 days, and decline to adult values over the next several weeks.(5)

Despite advances in the care of infants with hyperbilirubinemia, bilirubin toxicity is still a significant problem among neonates.(6) Bilirubin can cross the blood-brain barrier and enter the brain tissue if it is unconjugated or unbound to albumin. Asphyxia, acidosis, hypoxia, hypoperfusion, hyperosmolality and sepsis can damage the blood-brain barrier, allowing albumin-bound bilirubin to enter the brain tissue. The consequences of bilirubin toxicity are often devastating and irreversible. Hyperbilirubinemia may progress to kernicterus at any time during the neonatal period. If the infant survives the initial neurologic insult, chronic bilirubin encephalopathy may lead to developmental and motor delays, sensorineural deafness and mild mental retardation.(3,7)

The primary goal of effective and efficient management of neonatal indirect hyperbilirubinemia is to prevent acute bilirubin encephalopathy by lowering the

Original Article: Effect of Oral Zinc Supplementation on Neurodevelopment and Growth of Preterm Infants: A Meta-Analysis

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BACKGROUND

Zinc is an essential micronutrient that plays an important role in growth and development (Shaikhkhalil, 2014). It has a critical role in various functions of the human body including protein synthesis and nucleic acid metabolism, immunity and skeletal growth (Sonaware, 2014). It is an important cofactor of many enzymes and helps in the cellular and subcellular processes that are essential for cell proliferation, growth and brain development (Hafaez 2006, Hershkovitz 1999, Hoque 2009, Shakhkhalil, 2014, Sonaware 2014).

Zinc deficiency is a common and well-described problem in infants and children and leads to growth retardation, increased risk for infections, skin rash, immunological and endocrine dysfunctions, and poor neurodevelopment (Prasad 2013, Sunil 2010, Domeliof, 2014). The human body shows graded response to the degree of zinc deficiency; in mild zinc deficiency states a decrease in daily weight gain is detectable (Altigani, 1989). There is also some evidence suggesting that zinc deficiency in early childhood is associated with worse neuromotor development (Giles 2007).

Preterm neonates are especially vulnerable because of preterm delivery and low birth weight

(Islam 2009). They are also at increased risk of motor, neurological and language delay (Gong 2013). Hepatic zinc accumulation occurs during the entire gestation period, and preterm birth reduces the duration of pregnancy and thus the amount of hepatic stores available. (Domeliof 2014, Terrin 2015).

Other causes of impaired zinc status in preterm and low birth weight infants include low body stores (poor maternal fetal transfer and small liver size), limited capacity to absorb and retain micronutrients coupled with increased endogenous losses associated with immaturity of the small intestine and other organs, high nutrient demand to support catch up growth and inadequate intake of dietary zinc (Altigani, 1989, Friel 1985, Krebs 2006, Sunil 2010).

Measurement of serum zinc concentrations remains the best but imperfect marker to identify zinc deficiency (Terrin 2015). Low concentration of zinc was found in pre-term low birth weight babies in different studies (Islam 2009). They have lower zinc levels as compared with healthy term neonates especially during the first month of life when serum zinc levels rapidly decline (Terrin 2015, Higashi, 1985). Alkaline phosphatase is a zinc-dependent metalloenzyme that has also been used as a biological marker of zinc status and it is presumed to be lower in infants with zinc deficiency states (Shaikhkhalil 2014) and has been measured during zinc supplementation in various populations (Weismann, 1985).

Zinc has a major role in the developing brain by regulating neurotransmission in the hippocampus, rates of DNA, RNA and protein synthesis throughout the brain and IGF-1 gene expression (Ramel 2014). IGF-1 expression, in turn, regulates metabolic activity of neurons (RAMEL 2014). Insulin-like growth factor-1

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