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EXTENSIVE STUDY ON RETT SYNDROME: A CASE REPORT

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ABSTRACT: Rett Syndrome is an extremely rare, post-natal, and serious genetic neurodevelopmental syndrome that occurs mostly in female children. It occurs due to the mutations in the MeCP2 gene of the X chromosome. Children with Rett syndrome are usually diagnosed within 24 months of their age. The mutation takes place on the S421 site of the MeCP2 gene. The information for coding MeCP2 protein is obtained from the MeCP2 gene. This protein helps to silence or turn off the other genes. Thus, the mutation of the MeCP2 gene can disrupt the other genes and may interfere with the normal development of the Central Nervous System. The signs and symptoms of Rett syndrome may include slowed growth, brain growth slows after birth, loss of normal movement and coordination, loss of communication abilities, abnormal hand movements, unusual eye movements, breathing problems, irritability, crying, and other abnormal behaviors. There are 3 types of clinical criteria for the diagnosis of Rett syndrome. They are the main criteria, supportive criteria, and exclusion criteria. The doctor may recommend a genetic test to complement the diagnosis of Rett Syndrome. There is presently no cure for Rett syndrome. Symptomatic treatment with a multidisciplinary team is essential for the management of the clinical manifestations of the syndrome. With the MeCP2 gene as the target, the developing gene therapy aims to deliver a healthy copy of the mutated gene. Our study elaborates on the pathophysiology and management of Rett syndrome along with a case report.

INTRODUCTION: Rett Syndrome also called RTS or Cerebroatrophic hyperammonemia is an extremely rare, post-natal and serious genetic neurodevelopmental syndrome that occurs most commonly in a female child. Fewer than 5000 cases are being reported in India annually. It occurs due to the mutations in the MeCP2 gene of the X chromosome. It is usually diagnosed in the first two years of life. There is presently no cure for Rett syndrome.

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The disease was named after Dr. Andreas Rett, a pediatrician who discovered the syndrome in the 1960s [1].

Pathophysiology of Rett Syndrome [2, 3]: Rett syndrome is caused by a mutation in the methyl CPG binding protein [2] or known as the MeCP2 gene. This gene contains information for the synthesis of protein known as Methyl cytosine binding protein [2], which we say MeCP2 protein, and this protein is helpful in brain development. Also, this gene controls the functions of many other genes by acting as a molecular switch that helps turn on and off other genes' expressions and produce their unique proteins. Problems with this MeCP2 gene may result in defective MeCP2 protein production and thus cause abnormal expression of other genes. The MeCP2 gene, which

codes for MeCP2 protein, is located on the long arm of the X chromosome (Xq28). Every chromosome has a short and a long arm; the short arm is said to be the 'p' arm, whereas the long arm is called as 'q' arm, and the number indicates the band on the arm where the gene is located. So Xq28 refers to the band number 28 on the long arm of the X chromosome.

Neuronal Maturation in Rett Syndrome [4]: Normal neurons mature in their structure by developing a cytoskeleton, an axon, and dendrites with their branches. Functional maturation of the neurons is only possible when there is a synaptic contact of axons and dendrites with other neurons. This neuronal link is essential for the development, function, and continuity of the neuronal system.

The lack of this neuronal maturation is seen in Rett syndrome. Some immature neurons in many regions of the brain have been identified. This immaturity among neurons is seen as a deficiency of proteins associated with the mature cytoskeleton. There are a reduced number of dendritic branches for contact, or there are reduced sites at the axons for contact. Hence, the neurons are small and thus results in abnormality and immaturity of cellular neurochemistry.

This results in a small brain with immature neurons having a functional deficit depicting the neuronal abnormality in development. Comparing the brains of Rett patients and normal patients' brains showed that, Rett brains are 30% smaller in size compared to the normal brain, but their volume doesn't decrease with time. There is a significantly increased neuronal cell packing density (*i.e.)* the cell bodies of neurons are closer than they are in a normal brain. Neurons are reduced in size, branching is reduced, synapses are reduced, and column (arrangement pattern) size is also reduced in the cortex (in grey matter).

ABOUT MeCP2 [4, 5, 6, 7, 8, 9, 10, 11, 12, 13]: MeCP2 belongs to the family of methyl CpG binding domain (MBD) proteins that function as long-range transcriptional repressors that bind to methylated DNA and perform developmental silencing of other genes. Binding to the methylated DNA is facilitated through its transcription repressor domain (TRD) and its C-terminus. It is found that MeCP2 protein levels increase as the neurons mature, which explains the role of MeCP2 protein in the synaptic processes of mature neurons.

Knockout mouse models of two kinds were studied. One kind was those with defective MeCP2 function, which showed symptoms and features similar to Rett cases. Interestingly, even those models with overexpression of MeCP2 protein showed symptoms related to Rett Symptoms. This made a clear statement that both under-expression and over-expression of MeCP2 protein have more chances of developing Rett syndrome, and normal protein levels are only recommended.

In a recent study in an *in-vitro* overexpression model of RTT, phosphorylation of MeCP2 was conducted, and it was found that phosphorylation of MeCP2 protein at a particular amino acid residue S421, played a significant role in neuronal activity. S421 Site phosphorylation has been found to occur selectively in response to the activity of neurons. Mutation at this S421 site has blocked the ability of MeCP2 to restrict the functions like dendritic growth, maturation of the spine, and bndf transcription is activated, which is a calcium-dependent process. Thus, it is understood that when MeCP2 phosphorylation is triggered, there is neuronal connectivity in the nervous system mediated through the gene expression activated by the trigger. Mutations in the MeCP2 gene blocking this trigger also underlie the neural-specific pathology of RTT.

Symptoms of Rett Syndrome [14]: The symptoms of Rett syndrome usually occur after a normal delivery. The babies will have normal growth for the first 5 to 6 months after birth. They seem to behave normally at that period. The symptoms may develop after five months of age. The most characteristic symptoms of Rett syndrome, such as loss of communication, repetitive hand movements, breathing abnormalities and irritability, and crying, may develop during 12 to 18 months of age. The severity of symptoms can vary greatly from child to child.

Understanding the Concept [1, 2, 5]: Before discussing the different symptoms of Rett syndrome, it is very much important to have a quick review of the basic pathogenesis of Rett

syndrome. As discussed earlier, the MeCP2 gene is also called the 'housekeeping gene'. The mutation takes place on the S421 site of the MeCP2 gene. The MeCP2 gene codes for the MeCP2 protein. This protein helps to silence or turn off the other genes. Thus, the mutation of the MeCP2 gene can disrupt the other genes and may interfere with the normal development of the Central Nervous System. The MeCP2 gene helps in brain development specifically to establish neuronal connections. When the MeCP2 gene of one X chromosome undergoes mutation, the MeCP2 gene of the other X chromosome compensates for the functions. These MeCP2 genes will be enough for the brain's normal development during the first 5 months of age. As the baby grows, this MeCP2 gene will be insufficient for further development of the brain. The mutation can finally lead to impaired cognitive, sensory, emotional, motor, and autonomic functions. Our patient is an 18 months old female pediatric patient. She could not crawl when she was 5 months old. Now, she was also having trouble listening and issues regarding body balance. The symptoms of Rett syndrome usually occur due to the dysfunction and disruption in various portions of the brain. The functions of the respective parts of the brain are given in the image below.

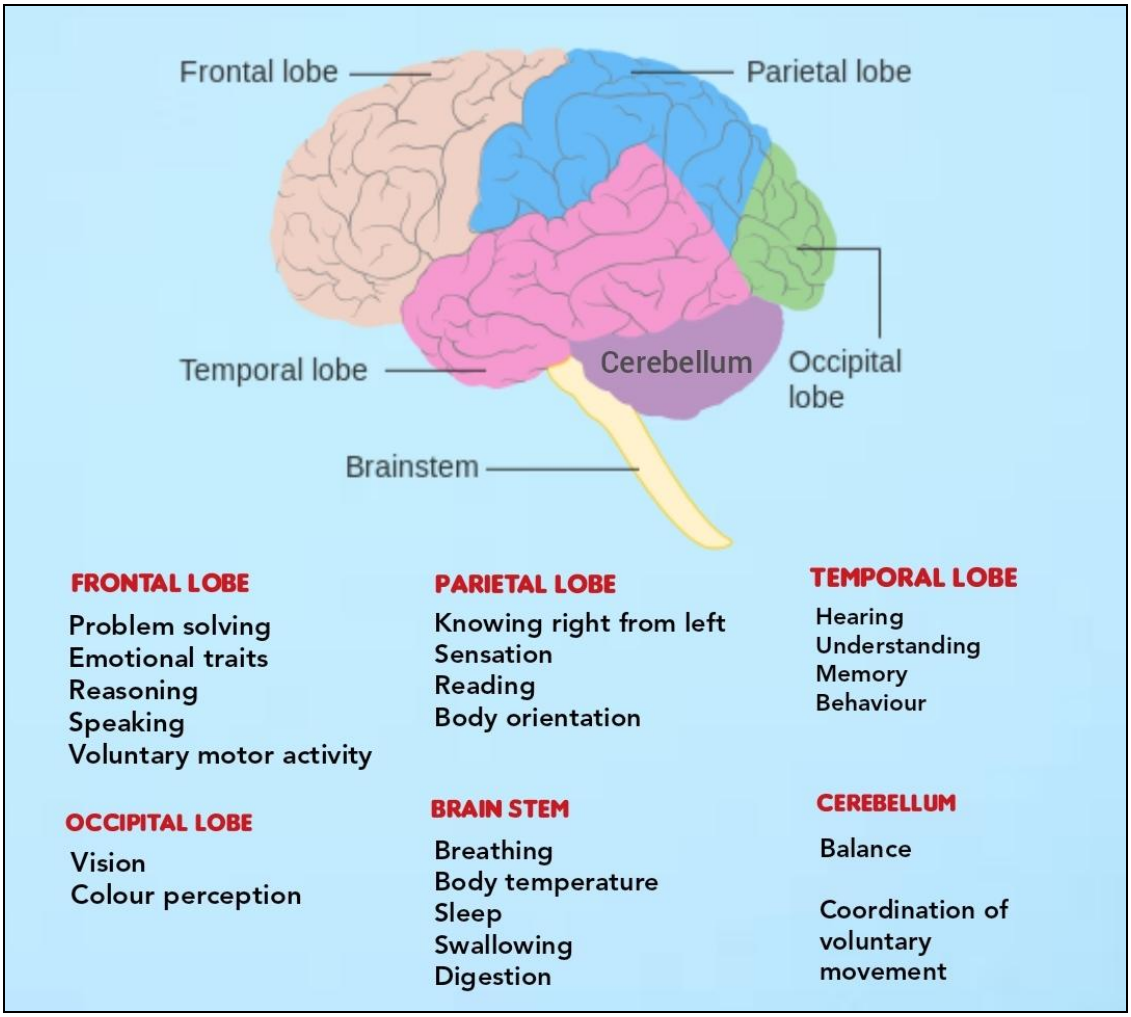

FIG. 1: FUNCTIONS OF VARIOUS PARTS OF THE BRAIN

The Signs and Symptoms of Rett Syndrome May Include [14, 15]:

- Loss of Coordinated movements: This will be the first symptom that occurs in a baby with Rett syndrome. This includes decreased ability to crawl. The baby may also show reduced hand control because of the gradual weakness in muscles.
- **Microcephaly:** Microcephaly (smaller head size) will be another characteristic symptom of Rett syndrome. As the baby grows, due to the

insufficient MeCP2 gene, the baby will show delayed growth or development in body parts.

- **Purposeless Hand Movements:** The most common symptom noted in Rett syndrome patients is repetitive hand movements without any purpose, such as clapping, rubbing, squeezing, and wringing hands unnecessarily.
- **Loss of Communication:** Children may gradually lose the ability to speak and make eye contact. Children with Rett syndrome may also show unusual eye movements such as closing one eye at a time, intense staring, and unusual or rapid blinking.
- **Hyperventilation and Other Breathing problems:** Due to the dysfunction of the brain stem, normal breathing is disrupted, and it may result in hyperventilation, swallowing of air, and forceful exhalation.

The other symptoms may include;

- Crying and screaming suddenly for no apparent reason.
- Cognitive disabilities.
- Seizures will be experienced by the patients at any stage of their life.
- Sleep disturbances like being awake at night or waking and crying suddenly at night.
- Scoliosis may occur after 8 years in a patient with Rett syndrome. Surgery will be required in such cases.

Stages of Rett Syndrome [14, 16]: The Rett syndrome is divided into four stages based on the development of symptoms. They are,

Stage I: Initial Symptoms: The signs and symptoms will not be unique, and it is difficult to diagnose these symptoms. The initial symptoms may develop between 6 to 18 months of age.

The signs and symptoms that may develop in this stage are;

- Loss of coordinated movements.
- Loss of communication and unusual eye movements.
- Loss of interest in toys.

The patient in our study is in the Initial stage and showed the above symptoms.

Stage II: Rapid Deterioration: This stage occurs between 1 to 4 Years of age. The symptoms that develop during this stage include;

- Microcephaly
- Delayed growth
- Further progression of Stage I symptoms

Stage III: Plateau Phase: This stage usually begins between 2 to 10 years and can last for several years. Seizures may occur in this stage. Some symptoms such as crying and irritability may get reduced in this stage, while other signs and symptoms will remain.

Stage IV: Late Motor Deterioration: This is the final stage and will occur after 10 in patients with Rett syndrome. The signs and symptoms of this stage are:

- Reduced movement
- Muscle weakness
- Scoliosis
- Communication and cognitive skills may improve slightly
- Repetitive hand movements may decrease
- Gazing usually improves

Diagnosis of Rett Syndrome [2, 17, 18, 19]: Rett Syndrome is diagnosed mainly by observing signs and symptoms of a child's early growth and development. A pediatric neurologist, clinical geneticist, and development pediatrician will diagnose Rett Syndrome. An electroencephalogram is frequently used to determine the type of seizure. A diagnosis of Rett syndrome may not be made for several years, because the syndrome is so rare and symptoms do not tend to appear until a child is between 6 and 18 months old. Sometimes it can be misdiagnosed as Prader-Willi syndrome, Angelman syndrome, Autism, or Cerebral Palsy.

A genetic test searching for MeCP2 gene mutation complements Rett Syndrome's clinical diagnosis.

There are 3 types of clinical criteria for the diagnosis of Rett syndrome:

- Main criteria.
- Supportive criteria.
- Exclusion criteria.

Main Criteria [20, 21]: In main criteria, it includes symptoms that must be present for a child to be diagnosed with Rett Syndrome.

Purposeless Hands movements such as (wringing, squeezing, clapping, rubbing), gait abnormalities, loss of acquired purposeful hand skills, post-natal deceleration of head growth, emerging social withdrawal, and communication dysfunction.

Supportive Criteria [20, 21]: In supportive criteria, some symptoms are not necessary for diagnosing Rett Syndrome but are present in people with the disorder. A child with symptoms from supportive criteria but no symptoms from main criteria does not have Rett Syndrome.

Delayed growth, small hands and feet, inappropriate laughing, reduced response to pain, intense eye communication or eye pointing, breathing problems such as hyperventilation and apnoea and air swallowing, teeth grinding, abnormal sleep patterns, poor circulation in hands and feet with cold and bluish to red hands and feet, abnormal muscle tone, scoliosis or kyphosis.

Exclusion Criteria [21]: A child with any of the following symptoms does not have Rett Syndrome. A neurometabolic disorder or other inherited degenerative disorder, a neurological disorder resulting from severe infection or head trauma, evidence of brain damage acquired after birth, crossly abnormal development in the first 6 months of life.

Genetic Testing [14, 21, 22, 23]: The doctor may recommend a genetic test to complement the diagnosis of Rett Syndrome. Most people with a clinical diagnosis of Rett syndrome (80 to 97 percent) have a change in this MeCP2 gene. However, even if a MeCP2 variation is found, the child may not be diagnosed with Rett syndrome if he or she doesn't experience the symptoms present in the main and supportive criteria. Thus, Rett syndrome should be diagnosed by observing the symptoms during their early developmental stage

The test is performed by drawing a small amount of blood from a vein in the arm. The blood sample is then submitted to a lab. This genetic screening is a blood test. Usually, it doesn't require any special preparation. After testing, the presence of a mutation in the MeCP2 gene confirms the diagnosis.

Recommended Comprehensive Testing for Rett Syndrome includes the following three tests:

- High-Density SNP Microarray Analysis.
- Next-Generation Sequencing.
- Targeted Deletion/Duplication Analysis

Management of Rett Syndrome: Though no cure is perfectly available for Rett syndrome yet, Symptomatic treatment is essential for managing the clinical manifestations of the syndrome. The management of Rett syndrome involves a multidisciplinary team approach that ensures regular monitoring of various aspects of the condition, such as assessing the degree of the already existing symptoms in patients, for their effective management. However, the ongoing research is expected for promising outcomes in providing a cure for Rett syndrome.

Pharmacological Management: Pharmacotherapy is essential for gaining control over symptoms such as seizures/epilepsy, gastro-oesophageal reflux, hyperventilation or breathing difficulties and motor disturbances and to provide essential nutrients through supplements.

Epilepsy [20, 24]: Seizures or epilepsy associated with the syndrome may require the lowest effective dose of conventional anti-epileptic agents such as Valproic acid or Carbamazepine or newer anti-epileptic agents as Lamotrigine or Topiramate, having the least side effects. Most of the anti-epileptic agents work by increasing the neuronal levels and enhancing the action of Gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, thereby exerting a direct

membrane-stabilizing action, inhibiting voltage-dependent sodium channels, causing repolarization and alteration in conductance, as a result of which repetitive firing of neurons is inhibited.

Gastro-Oesophageal Reflux [24, 25, 26]: A prokinetic agent such as Metoclopramide may aid in the management of gastro-oesophageal reflux in patients with Rett syndrome. Dopamine usually decreases gut motility and may induce nausea, vomiting, or gastro-oesophageal reflux by stimulating the medulla oblongata's chemoreceptor trigger zone (CTZ). Metoclopramide is a dopamine antagonist that increases gut motility and speeds food movement through the gastrointestinal tract. It is also known to augment the activity of Acetylcholine, which could cause a slower heart rate and help certain patients who have increased heart rate associated with the condition. However, Metoclopramide should not be taken longer than 12 weeks.

Hyperventilation [20]: Naltrexone, 1mg/kg, or Magnesium citrate or orotate up to 10mg can be used effectively to help with hyperventilation, rapid breathing, or apnoea in patients with Rett syndrome.

Constipation [20]: Fiber supplements such as Methylcellulose or Psyllium that exert a laxative effect are usually recommended. These prevent the stool from becoming hard and aid in patients having constipation.

Energy Supplementation [20, 24, 27, 28, 29]: Certain amino acid derivatives of Lysine and Methionine are vagal nerve stimulators, essential for energy metabolism and excretion of excess fatty acids. Carnitine is a proteinaceous carrier molecule involved in transporting long-chain fatty acids into the mitochondria and its metabolism in the mitochondria for deriving energy.

It also exports acyl groups from the cells and sub-cellular organelles and flushes them out in the urine, preventing their accumulation. Carnitine is usually synthesized in the body from amino acids Lysine and Methionine provided by dietary meat and dairy products, for which Vitamin C is essential. Carnitine levels less than 20µmol/L of plasma concentration are considered Carnitine deficiency. Since Carnitine is a constituent of the liver and striated muscle, Carnitine deficiency may cause liver, heart, or other muscle problems, brain dysfunction, *etc*. Levo-Carnitine 30ml/day can be given to prevent or treat Carnitine deficiency in patients with Rett syndrome.

Vitamin Supplementation [29]: Osteoporosis or Vitamin D_3 deficiency is prevalent in patients having Rett syndrome. Hence, Vitamin D_3 (Cholecalciferol) 1 ml containing 400 I.U. can be used as a prophylactic or to treat deficiency of Vitamin D_3 essential for the provision of good bone and muscle health.

Non-Pharmacological Management [20, 31]: Flashcards or Communication boards with printed words and pictures may be used amongst the directions from a speech therapist to enhance communicative skills. Physical and Occupational therapists ensure the provision of knowledge and practice regarding body positioning and adaptive equipment such as braces or splints that may aid in managing kyphosis or scoliosis. However, certain patients may require surgery to correct scoliosis. Supine, elevated supine, prone resting, prone on forearms, quadruped on forearms, side-lying, kneeling, and supported standing are the most commonly recommended. Music therapy, Massage therapy, Hydrotherapy, and Hippotherapy have also found their use in Rett syndrome.

Food and Nutrition [20]: A Ketogenic diet, rich in fat, having a minimal amount of protein and the least or no carbohydrate content is preferred to benefit seizure control. Thickened feeding solutions and an upright position during and after feeding are recommended to avoid gastro-oesophageal reflux. Fiber-rich foods help in managing constipation.

Gene Therapy [20, 24, 30, 31]: With the MeCP2 gene as the target, the developing gene therapy aims to deliver a healthy copy of the mutated gene using the AAV 9 viral vector, capable of penetrating the Blood-Brain Barrier, to the nerve cells.

AveXis was in the way of developing the AVXS-201 gene therapy for Rett's syndrome, which has been bought by Novartis, planning to seek approval by the U.S. FDA (Food and Drug Administration) in 2022. MeCP2 gene produces a protein that regulates the downstream genes that play critical roles in brain function. Hence, the gene therapy

must ensure a cautious balance of expression of the MeCP2 protein, which may otherwise result in a much debilitating condition called the MeCP2 Duplication Syndrome.

Case Report:

Chief Complaints: Our patient is an 18 months (1.5 years) female pediatric patient diagnosed with Rett syndrome at 5 months of age by her parents, while she could not crawl. Presently she has trouble listening and issues regarding body balance.

Past Medical History: Could not crawl from 5 months of age.

Past Medication History: NIL

Family History: No significant family history.

Diagnosis: The patient was initially diagnosed through the patient history provided by her mother when she could not crawl. The physical examinations suggested impaired coordination, trouble in listening, and issues regarding body balance.

Investigation: Genetic DNA blood Test - MeCP2 gene mutations in the X chromosome (Xq28) were found in the patient.

Assessment: From the subjective evidence and the performed investigations, the patient was diagnosed to have Rett syndrome.

Treatment Goals:

- Rett syndrome cannot be cured but, management of signs and symptoms might help.
- A multidisciplinary team approach involving pharmacological and non-pharmacological measures with regular monitoring is essential for the symptomatic management of the condition.
- To improve coordinated movements.
- To slow down the further progression of the disorder and improve the quality of life.

Treatment:

Brand Name	Generic Name	Route	Dose	Duration
Carnitor Syrup	Levocarnitine syrup	Oral	30 ml/day	TID
Clomet	Metoclopramide syrup	Oral	1 ml	TID
Uprise-D	Vitamin D3 syrup	Oral	400 IU	OD

Physiotherapy:

- Regular standing with or without a standing frame to improve balance, maintain bone density and stretch muscles.
- Repositioning in prone lying, long sitting, and prone sitting improves posture and increases comfort.
- Gait re-training.

Treatment Outcomes:

- The infant was able to crawl.
- Improved ability of the infant to stand with external support.
- The gastro-esophageal reflux was treated.
- Improved coordinated movements.
- Improved social interaction.

Follow Up and Plan:

- Levocarnitine and physiotherapy are continued.
- Regular monitoring is required to check for scoliosis and newly evolved symptoms of the condition.
- Gene therapy has been developed for Rett Syndrome by AveXis and is under clinical trials. If it gets approved, this could cure the patient.
- If any other symptoms occur, symptomatic management can be done.

Patient Counselling:

- Use pictures and letters to communicate.
- Proper nutrition is extremely important for normal growth and improved mental, physical and social abilities. The ketogenic diet may be helpful.

- Animal-assisted therapy or pet therapy may improve social awareness.

- To prevent gastroesophageal reflux, thickened feeding solutions and semi-upright positions after feeding will aid to prevent gastroesophageal reflux.

DISCUSSION: As we have seen above, the mutation in the gene can be cured only by replacing the mutated gene with a healthy one. The Avexis team has proposed this replacing gene approach as AVXS- 201. This AVXS-201 is a gene therapy technique that uses a vector virus AAV9 to deliver the healthy gene to the targeted nerve, and since it can easily cross the blood-brain barrier, the virus can reach brain neurons to deliver the gene. This technique is hoped to save many lives that we have been losing without a solution.

CONCLUSION: The extensive study on Rett Syndrome focuses on various stages and the associated signs and symptoms and modalities of management, emphasizing the pronounced pathophysiology of the condition, along with a case report.

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