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# Treatment of Angelman Syndrome: An Educational Article and Expert Opinion

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## ABSTRACT

**Background:** Angelman syndrome, historically termed "happy puppet syndrome," is a rare neurodevelopmental disorder characterized by severe mental retardation, epilepsy, ataxic gait, and a distinctively happy demeanor. Since its first description by Harry Angelman in 1965, the syndrome has been recognized worldwide, though reports from Iraq have been absent due to limited genetic diagnostic infrastructure and awareness. **Objective:** To present the first documented case of Angelman syndrome in Iraq, detailing its clinical, neuroimaging, and therapeutic features, and to highlight the significance of structured clinical recognition and management of rare genetic disorders in the region. **Patients and methods:** A 21-year-old Iraqi female with lifelong developmental delay, epilepsy, and characteristic behavioral and craniofacial features was clinically evaluated. Developmental, neurological, and family histories were obtained. MRI of the brain was performed using axial T1, DWI, FLAIR, and T2-weighted sequences. The patient was treated with a multi-modal regimen targeting seizure control, cognitive function, and neuroprotection, including lamotrigine, acetazolamide, citicoline, piracetam, cerebrolysin, and nutritional support. **Results:** The patient exhibited hallmark features of Angelman syndrome: frequent laughter, moderate mental retardation, severe speech impairment, puppet-like gait, and characteristic craniofacial dysmorphism (long narrow face, flat occiput, wide mouth, irregular teeth, and strabismus). MRI demonstrated high T2/FLAIR signals in periatrial and occipital white matter with parieto-occipital atrophy and mild ventricular dilatation, consistent with demyelinating changes previously described in Angelman syndrome. After switching from valproate to lamotrigine (100 mg twice daily), seizures ceased. Adjunctive therapy with citicoline, piracetam, cerebrolysin, acetazolamide, and nutritional supplementation led to improve speech gains, gait impairment persisted. **Conclusion:** This case represents the first confirmed report of Angelman syndrome in Iraq. The patient's clinical and MRI findings align with international descriptions of Angelman syndrome. The observed therapeutic response particularly

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to lamotrigine and adjunct neurotrophic agents supports their potential benefit in managing epilepsy and cognitive dysfunction in Angelman syndrome. The report underscores the importance of developing clinical genetics capacity in Iraq for improved recognition and management of rare neurodevelopmental disorders.

**Keywords:** Angelman Syndrome, Treatment, Educational Article, Expert Opinion

## INTRODUCTION

Angelman syndrome, also historically known as "happy puppet syndrome", is a dysmorphic neurodevelopmental disorder associated with severe mental retardation, seizures, gait abnormalities, and a distinctively happy personality [1-5].

The syndrome was first described by Harry Angelman (Figure-1), a British pediatrician, who reported three children with the condition in 1965 [1]. These children exhibited mental retardation, an unusually happy personality, brachycephaly with microcephaly, weakness of the limbs, and epilepsy.

**Figure 1.** Harry Angelman (1915-1996), British pediatrician, first described Angelman syndrome.

Subsequent reports expanded the clinical spectrum. Dooley et al. (1981) reviewed twenty-two previously described patients and reported five new cases, noting severe mental retardation, epilepsy, puppet-like ataxic movements, microbrachycephaly, prognathism, tongue protrusion, and inappropriate paroxysms of laughter [3].

In 1982, Williams and Frias studied six patients and emphasized the cardinal features: severe mental retardation, puppet-like gait, characteristic craniofacial dysmorphism, and frequent laughter episodes [4].

By 1986, Pascual Pascual et al. highlighted Angelman syndrome as a condition of unknown etiology with only about 50 reported cases worldwide, affecting both sexes across races and continents. They described three additional cases [5].

Since its first description by Harry Angelman in 1965, the syndrome has been recognized worldwide, though reports from Iraq have been absent due to limited genetic diagnostic infrastructure and awareness.

**Here, we report the first documented case of Angelman syndrome in Iraq, presenting detailed clinical features, MRI abnormalities, and response to innovative therapy.**

## PATIENTS AND METHODS

A 21-year-old girl with mental and growth retardation (weight 35 kg, height 141 cm) was evaluated.

Developmental history

- Global developmental delay in early childhood with late walking and delayed speech.
- Despite poor speech, she was able to communicate interactively.
- At age 21, she required assistance for eating and toileting.

**Neurological features**

- Poor, unstable "puppet-like" gait.
- Epilepsy partially controlled with valproate 1000 mg/day (two seizures per month).
- Carbamazepine was discontinued due to abnormal movements.
- Episodes of inappropriate laughter.
- Unable to name colors, identify or copy shapes (circle), or stand on one leg.
- Limb weakness was present.

**Family history**

- Two sisters died at 3 days of age, reportedly due to maternal toxoplasmosis ("cat disease").
- Patient herself had neonatal illness, father was told she had brain hemorrhage.

**Physical and craniofacial features (Figure-2)**

- Long, narrow face with flat occiput.
- Wide mouth with thin upper lip and irregular, widely spaced teeth.
- Prominent nasal bridge.
- Deep-set eyes with mild strabismus.

**Figure 2.** The patient has craniofacial dysmorphic features including long, narrow face, wide mouth with thin upper, irregular, widely spaced teeth, prominent nasal bridge, and deep-set eyes with mild strabismus.

## RESULTS

The diagnosis of Angelman syndrome was made based on:

- Characteristic happy/social demeanor (Figure-2) with frequent laughter.
- Moderate mental retardation with interactive communication.
- Epilepsy partially controlled with valproate.
- Puppet-like gait and motor incoordination.
- Distinctive craniofacial phenotype (Figure-2).

**MRI Examination of the Brain Technique:**

Axial T1 DWI, FLAIR, and T2 weighted images; sagittal and coronal FLAIR images.

**Findings:**

- High T2 and FLAIR signals in periatrial and occipital white matter extending into the splenium of the corpus callosum (no diffusion restriction).
- Atrophy of both parietal and occipital lobes with mild dilatation of the occipital horns and atrial parts of the lateral ventricles.
- Nonspecific deep white matter lesions suggestive of demyelination.
- Normal brainstem, cerebellum, pituitary gland, and suprasellar region.
- No midline shift.

**Treatment and Clinical Course**

The focus of treatment was controlling seizures, improving cognitive skills and motor function. Treatment plan was designed based on our extensive published experiences with treatment of seizures, mental retardation, brain atrophy and other neurological conditions [6-14]:

**First week**

Lamotrigine was started in a dose of 100 mg twice daily with gradual withdrawal of valproate over few days.

Oral acetazolamide (Diamox) 250 mg once daily.

Intramuscular piracetam 800 mg daily for one week.

Oral citicoline 200 mg daily in the morning.

Treatment was associated with some improvement and no seizure was reported despite stopping valproate.

**Second week**

Lamotrigine 100 mg twice daily.

Oral acetazolamide (Diamox) 250 mg once daily plus potassium supplementation (Serum potassium 3.4 meq/L just below the lower limit of 3.4 meq/L.

Oral citicoline 200 mg daily in the morning.

Oral piracetam 800 mg daily in the morning.

Intramuscular cerebrolysin 5 ml daily for one week.

Treatment was associated with cessation of seizures and more improvement in speech, but most of her speech was still not understandable to the doctor despite the father was understanding easily and very well. No obvious improvement in gait and she still has difficulties in holding a pen and was unable to name colors.

**Third week**

Lamotrigine 100 mg twice daily.

Oral acetazolamide (Diamox) 250 mg once daily plus potassium supplementation (Serum potassium 3.4 meq/L just below the lower limit of 3.4 meq/L.

Oral citicoline 200 mg daily in the morning.

Oral piracetam 800 mg daily in the morning.

Intramuscular cerebrolysin 5 ml daily for one week.

Royal jelly capsule (Nutritional supplement) twice daily.

Nandrolone decanoate single intramuscular of 25 mg.

## DISCUSSION

Magnetic resonance imaging (MRI) of the brain in this 21-year-old female demonstrated areas of high T2 and FLAIR signal intensity within the periatrial and occipital white matter, extending into the splenium of the corpus callosum, without diffusion restriction.

These changes were associated with atrophic changes in both parietal and occipital lobes and mild dilatation of the occipital horns and atrial parts of the lateral ventricles. In addition, non-specific deep white matter lesions were noted, suggestive of ischemic demyelination.

The imaging findings in this case, when correlated with the clinical phenotype, are most consistent with Angelman syndrome. The patient exhibited a happy social demeanor, frequent laughter episodes, speech impairment, moderate mental retardation, epilepsy partially controlled with valproate, poor unstable gait with a "puppet-like" quality, global developmental delay, and craniofacial dysmorphism including long narrow face, wide mouth with irregular teeth, strabismus, and a flat occiput.

Reports in the literature describe variable MRI abnormalities in Angelman syndrome, including cerebral atrophy, parieto-occipital predominance of white matter signal changes, and involvement of the corpus callosum, which reflect abnormal myelination and neurodegenerative processes [3,4]. The findings in this Iraqi patient are in keeping with these observations.

The switch from valproate to lamotrigine led to cessation of seizures, in line with evidence suggesting better efficacy and tolerability of lamotrigine in Angelman syndrome [15,16].

Therapeutically, our approach aligned with evidence:

- Tang et al. (2017) found lamotrigine superior to valproate when monotherapy with the latter fails [15].
- Samanta (2021) emphasized the advantage of lamotrigine due to its favorable side-effect profile compared to valproate [16].

The adjunctive use of neuroprotective and nootropic agents (citicoline, piracetam, cerebrolysin, acetazolamide, and nutritional support) was associated with improved interaction and some language progress, though gross motor dysfunction persisted. Therefore, nandrolone decanoate was added based on available evidence [10-12,14].

Piracetam beneficial effects on impaired cerebral functions include improving neuronal and cognitive functions, increasing cerebral blood flow and oxygen consumption, improving neurotransmitters function and brain neurotransmission. Piracetam is not associated with important side effect nor has acute toxicity at the therapeutic doses. Piracetam has been used with important benefits in the treatment of cerebral palsy and other childhood neuro-psychiatric disorders [17,18].

Citicoline is a safe form of the choline has been increasingly grouped with the water soluble B vitamins. It has been increasingly used with noticeable benefits in the treatment of several pediatric and neuro-psychiatric disorders including, cerebral palsy, cognitive impairment, autism disorders, Rett syndrome, and kernicterus [19,20].

Cerebrolysin is a mixture of free amino acids (85%) and 15% biologically active low molecular weight amino acid sequences which include low molecular weight neuro-peptides (Brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, nerve growth factor, ciliary neurotrophic factor [21-28].

Cerebrolysin has been used safely with benefit in a variety of neuro-psychiatric disorders including idiopathic mental retardation, cerebral palsy, brain atrophy, myelomeningocele, pediatric juvenile spinal muscular atrophy, pediatric Charcot Marie Tooth disease, kernicterus, and agenesis of corpus callosum with colpocephaly [29-31].

Nandrolone decanoate is known to have a useful muscle strengthening effects, and has been used with noticeable benefit in the treatment of cerebral palsy, refractory vitamin D-resistant rickets, and achondroplasia. It is not 17-testosterone derivatives, and therefore nandrolone esters are not associated with sodium sulfobromophthalein retention; therefore, liver complications are not a risk when used for short periods [9,30-32].

**Since its first description by Harry Angelman in 1965, the syndrome has been recognized worldwide, though reports from Iraq have been absent due to limited genetic diagnostic infrastructure and awareness.**

For many decades, the fields of clinical genetics and dysmorphology were largely absent from the Iraqi medical landscape.

There were no structured diagnostic pathways, no specialized centers for rare diseases, and minimal local literature to support genetic awareness or dysmorphic diagnosis. As a

result, generations of patients with congenital abnormalities and inherited disorders remained undiagnosed or misclassified.

The transformation began with our early clinical observations in pediatric practice, which led to the recognition of patterns suggestive of specific syndromes. Gradually, through careful phenotyping, clinical photography, and correlating systemic findings with existing global data, we began to document and publish rare and very rare disorders observed among Iraqi children.

Common genetic and hereditary disorders in Iraq include the thalassaemias and hemophilias, for these disorders specialized clinics and centers have been established. In addition to Down syndrome which has been reported frequently, many other less common disorders have also been reported including polycystic kidney disease, achondroplasia, Duchenne muscular dystrophy, Werding Hoffman disease, Gaucher disease, mucopolysaccharidosis.

We have previously reported an uncountable number of the first described disorders in Iraq [33-34].

This case represents the first documented report of Angelman syndrome in Iraq with characteristic clinical features and supportive MRI abnormalities, reinforcing the value of integrating imaging with careful clinical assessment in the evaluation of syndromic developmental disorders.

## CONCLUSION

This case represents the first confirmed report of Angelman syndrome in Iraq. The patient's clinical and MRI findings align with international descriptions of Angelman syndrome. The observed therapeutic response particularly to lamotrigine and adjunct neurotrophic agents supports their potential benefit in managing epilepsy and cognitive dysfunction in Angelman syndrome. The report underscores the importance of developing clinical genetics capacity in Iraq for improved recognition and management of rare neurodevelopmental disorders.

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## CONFLICT OF INTEREST

None.

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