

## Two anesthetics in a pediatric patient affected from undiagnosed Angelman syndrome

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### Key points

Angelman syndrome (AS) is the clinical expression of abnormalities of chromosome 15, involving impairment of a subunit of the gamma-aminobutyric acid (GABA) receptor. Although the syndrome is well described in medical literature with its potential anaesthetic implications, it's necessary to keep attention to undiagnosed rare diseases.

### Abstract

A case of a male child who undergone two interventions (pylorotomy at about two months of age, bilateral orchidopexy and clearing of glans penis adhesions at two years), both of them were conducted in ignorance of the underlying genetic disease is presented. All two the perioperative periods were uneventful. After a review of literature relating to AS, a few suggestions are presented.

**Keywords:** Angelman syndrome; rare disease; anesthesia

### Introduction

AS is a distinct neurogenetic syndrome first described by Harry Angelman in 1965 [1] as a “puppet children”, later on it was suggested [2] the eponymous “Angelman” in order to avoid any possible offence to the families of affected persons. Different genetic mechanisms [3] may cause AS, such as deletion or re-arrangement of the maternal chromosome 15 at locus 15 q11.2-q13 (60-75%) with a more severe phenotype [4]. A small percentage of patients (2-5%) have paternal uniparental disomy with milder clinical phenotype; mutations in the imprinting centre are present in 2-5% and mutations in the UBE3A gene in 10%. In a group of 5 -26% with the classical phenotype the genetic defect

remains unidentified[3,5]. Imprinted genes pathology examples are represented by the Prader-Willi and Angelman syndromes, whose phenotypes result from loss of paternal or maternal contributions of 15 q11-q13 genomic region, respectively [6]. As a result there is a defect in genetic coding in GABA-A receptors, disorders of synthesis and release of GABA with unpredictability of anaesthetic agents acting on these receptors.

Criteria for the clinical diagnosis of AS were put forth in 1995 and updated 10 years later in light of subsequent research [7,4]. There is no scoring system or diagnostic threshold, though these features can guide the clinical diagnosis.

Characteristic symptoms :

- developmental delays, functionally severe, such as lack of crawling or babbling at 9 to 12 months, mental retardation
- speech impairment (lack or minimal)
- movement or balance disorders (ataxia or gait)
- trembling movement of limbs
- frequent involuntary smiling and laughter
- happy, excitable personality, often with uplifted hand flapping or waving movements

Other signs and symptoms include: seizures (onset usually before three years of age), stiff or jerk movements, microcephaly, flatness in the back of head, tongue thrusting, sucking/swallowing disorders, strabismus, prognathia, abnormal sleep-wake cycles, drooling, increased sensitivity to heat, fascination with water and crinkly items, truncal hypotonia in infancy, in adult obesity and scoliosis. Anaesthesia related features include structural cardiac abnormalities [8], muscular atrophy [9], bradycardia and cardiac arrest resulted from dominance of vagal tone [9,10], despite asystole was reported even during normal bouts of laughter[11], relative insensitivity to pain [12], seizures [13].

### **Case report**

Neither in parents nor in relatives medical history hereditary defects were found in our patient coming from common pregnancy, full term, no complications at birth (weight 3,380 kg). At sixtythree days of life he was admitted to hospital in paediatricward for regurgitations, diarrhoea, poor growth gain (4,450 kg) and suspicious allergic rash. During the following days more frequent (enhanced) regurgitations and projectile vomiting were observed. Ultrasound corroborated the clinical hypothesis of pyloric stenosis with slight opening of alimentary canal (2-2,5 mm). Abdominal direct X-ray with barium described a pronounced gastro-oesophageal reflux, stringy lumen of the canal, slow transit in duodenum. A pylorotomy was planned. No features of AS were detected and physical examination was unremarkable. After draining of the stomach via a orogastric tube an inhalational anaesthesia was induced with oxygen, air and sevoflurane, he was given cisatracurium (0,15 mg.kg-1) to facilitate tracheal intubation with a 3,5 mm uncuffed tube after two minutes of gentle mask ventilation. Anaesthesia was maintained with oxygen, air, sevoflurane 2% and remifentanyl (0,15-0,25  $\mu$ /kg.min-1). With periumbilical incision, at the end of surgery was performed a rectus sheath block. The procedure lasted about forty minutes and perioperative period was uneventful. At eight

months of age parents noticed a psychomotor delay in developmental behaviour (first warning sign was neck muscles hypotonia) and seizures. Magnetic resonance imaging pointed out a mild cerebral cortical atrophy with common EEG pattern.

At the age of two the boy was scheduled for bilateral orchidopexis and clearing of glans penis adhesions. He took valproic acid for seizures and levotiroxine for autoimmune hypotiroidism. In the light of foregoing anaphylatoid shock to kiwi total operating theatre was set up latex-free. Anaesthesia was induced and maintained with propofol 7mg/kg/h-1 in oxygen and air, remifentanyl 0,15-0,25  $\mu$ /kg.min-1, neuromuscular blockade was induced with mivacurium 0,18 mg.kg-1. For intra and postoperative analgesia it was opted for caudal anaesthesia with bupivacaine 0,25% and clonidine 10  $\mu$ . Having compared the two anaesthetic records, monitoring (ECG, SpO<sub>2</sub>, NIBP) was similar, heart rate and blood pressure never outnumbered the 20% of baseline, SpO<sub>2</sub> was stable throughout. At about the age of three a diagnosis was eventually settled with Angelman syndrome. Cariotype 46, XY, ish del(15)(q11-q13)(D15S10-). Such deletion is present in more than 60% of patients. It was beared out with methylation molecular survey in 15q11-13 area by PNO.9 probe.

### **Discussion**

To the best to my knowledge, there are only a few articles pertaining to anaesthesia related literature and AS [9,10,14,15,16,17]. This is the first case reported of a patient not diagnosed with AS who undergone two surgical operations, in addition/moreover the first one at two months of life, the youngest age detected until now. Traditionally, general anaesthetics were believed to act in a non-specific manner, but such theories have now been superseded with evidence of highly stereo-selective interactions between general anaesthetics and select proteins found within the CNS. Transmitter gated ion channels represent one such group of proteins and have been found to be sensitive to modulation by a

range of chemically diverse anaesthetic agents. There is a family of genetically related ion channels including inhibitory GABA-A receptors, strychnine-sensitive glycine receptors and excitatory neuronal nicotinic receptors. However, current consensus favours GABA-A receptors as the principal target because almost all general anaesthetics, with the exception of ketamine and xenon, enhance receptor activity. These receptors mediate the majority of fast inhibitory neurotransmission within the cerebral cortex therefore they represent logical targets for general anaesthetic drugs. In particular intravenous general anaesthetics should work on  $\beta$  subunit, whereas inhalational ones on  $\alpha$  subunit likely not affected in AS [16,18]. With regard research papers (literature), by now assumed the main role of impaired GABA receptors, there is still ambiguity about the best anaesthetic management in AS, considered the incidence of it (1/15000-20000 births), low but not extremely rare. It's quite unusual that referential literature was so lacking, unless the great majority of surgical operations (dental, orthopaedic) had not been performed deeming the patient

just a psychologically disabled child or rather the procedure was uneventful. On the one hand there are ones who promote intravenous anaesthesia [9], recommending propofol and fentanyl derivatives (no interference with GABA system), given the influence of halogenated ethers on GABA receptors that is the activation of extrasynaptic structures and resulting change in the polarization of brain cells, as well as inhibiting their activity, along with the suggestion that presynaptic uptake systems for various neurotransmitters, including GABA, may be the molecular targets for volatile anaesthetic gases, and not supporting the hypothesis of exerting their action via specific inhibition of GABA uptake [19]. These supporters [9] advised to significantly limit the use of benzodiazepines and halogenated, despite their use of sevoflurane for maintenance. Remarkable, even for a

short time, severe bradycardia with delayed reaction to atropine was observed. Recovery was judged markedly prolonged.

Halfway we found [15], who managed the patient with propofol, ketamine induction and sevoflurane, oxygen and air with small doses of fentanyl for maintenance, via several receptors (GABA-A, N-Methyl-D-Aspartate NMDA and opiates). This case was uneventful. On the other hand the remaining ones [10,14,16,17] opted for gaseous intraoperative anaesthesia.

Difficulties respectively reported: bradycardia [10] shifted/turned in asystole during pneumoperitoneum (successful CPR) and chaotic respiratory pattern/insufficiency [17] at emergence. It's worthwhile recall that formerly in year 2000, AS was taken into account [13] only in terms of epilepsy and continuing current anticonvulsants, delineating genetic diseases and risks for anaesthesia complications, three years before first report [14]. From then on nothing about AS. Discussing about seizures and anaesthetic drugs in 2008, [20] state that on the basis of applied neuropharmacology, prevention of anaesthetic-drug related seizures would include 1) use cautiously sevoflurane at a maximal concentration limited  $< 1,5$  MAC, avoid etomidate  $\beta_2$ - $\beta_3$  agonist, 2) considering prophylaxis with adjunctive benzodiazepines or drugs (gabapentin, NMDA-blockers as xenon, nitrous oxide, ketamine) that impair calcium entry into neurons, and 3) propofol remains an enigma and its safe use remains controversial.

The only reference concerning AS [21] raises awareness about drugs actions on  $\beta_2$  vs  $\beta_3$  receptors, it's likely these patients were susceptible to etomidate (or propofol) induced seizures, opposed to benzodiazepines which act on mainly  $\alpha$  GABA-A subunits.

There is still a grey area about the best anaesthetic management in Angelman syndrome: no reports of a total intravenous anaesthesia (propofol for maintenance) and of locoregional anaesthesia before this work was published.

It's appropriate, that being so, suggest some advices concerning anaesthesia in Angelman syndrome:

- maintenance of antiepileptic treatment [16,20]
- close vigilance of cardiac rhythm (vagal hypertonia) [9,10]
- NMDA blockers as ketamine or nitrous oxide [15,17,20]
- sevoflurane has been used in any case [9,10,14,15,16,17]
- opioids: no troubles pointed out
- neuromuscular monitoring (peripheral muscular atrophy) [9,16]
- a recent review [22] didn't find neither exaggerate response to GABA stimulating drugs, nor perioperative anesthetic-related complications

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