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# Anesthesia for patients with Rett syndrome: a systematic review

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**Abstract**: Ret syndrome a rare neurological syndrome that affects 1 in 10.000 female children. Patients with Rett syndrome receiving anesthesia are prone to develop respiratory complications.
*Methods*: A systematic review was conducted to critically review the available literature on Rett syndrome. Results: Difficult airway management was found in only a minority of cases. Patients with Rett syndrome are more likely to have respiratory complications after spinal fusion surgery and have a longer mechanical ventilation time and longer postoperative ICU stay. Major respiratory events can occur even when undergoing minor procedures. Differences in nociception might exist in patients with Rett syndrome resulting in some patients with decreased analgesic requirements. Neuraxial anesthetics techniques are possible despite the high incidence of scoliosis. Patients with Rett syndrome seem to have increased sensitivity to side effects of opioids, even when administered epidurally or intrathecally. QT-prolonging drugs should be avoided due to frequent long QT-interval in patients with Rett syndrome. Succinylcholine is not recommended in Rett syndrome due to its QT-elongating effect and risk of hyperkalemia in immobilized patients. The use of a cholinesterase inhibitor and an anticholinergic drug for reversal of neuromuscular blockade is also not recommended due to its QT-elongating effect. Sugammadex, due to its negligible effect on QT-interval should be considered when reversal of neuromuscular blockade by rocuronium is indicated.

**Keywords**: Anesthesia; Rett syndrome.

## Introduction

Rett syndrome is a rare neurological syndrome that affects 1 in 10.000 female children (1, 2). In 90 to 95 % of cases a loss-of-function mutation in the MECP2-gene on the X-chromosome is found (1). The syndrome is characterized by normal early development followed by loss or stagnation of acquired cognitive, verbal and motor skills (1). Stereotypical hand movements, gait abnormalities, loss of language and hand skills typically develop and are major diagnostic criteria (3). There is no fundamental cure for Rett syndrome. Gene therapy, aiming to introduce a functional MECP2-gene, might play an important role in treating these patients the future (4). Scoliosis is an important comorbidity in Rett syndrome, up to 75% of children with Rett syndrome develop scoliosis by the age of 15 years (5). In about 20% of cases spinal fusion surgery is indicated (6). Other surgical or medical procedures that may be necessary for these patients are dental procedures, cholecystectomy, placement of a gastrostomy, tonsillectomy, adenoidectomy, surgery for hip displacement and contracture release (7). Therefore, a significant proportion of Rett syndrome patients will require anesthesia. Delayed gastric emptying, breathing irregularities, long QT syndrome and epilepsy are all associated with Rett syndrome (8) and should be considered when providing anesthesia for these patients. Patients with Rett syndrome have a higher risk of prolonged apnea when receiving sedation (9), posing additional challenge in providing safe anesthetic care to this specific population.

Our aim is to critically review the available literature on Rett syndrome and anesthesia and to guide clinicians in providing anesthesia to this patient population.

## Methods

A literature search was conducted searching the EMBASE, PubMed and Cochrane Database.

Search terms related to anesthesia and perioperative care were identified by the authors. The used search terms were “Rett syndrome” AND “anesthesia” OR “propofol” OR “hypnotics” OR “sedation” OR “benzodiazepines” OR “midalam”

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OR “diazepam” OR “clonidine” OR “dexmedetomidine” OR “ketamine” OR “nitrous oxide” OR ”sevoflurane” OR “desflurane” OR “isoflurane” OR “halothane” OR “opioids” OR “morphine” OR “sufentanil” OR “fentanyl” OR “remifentanil” OR “ alfentanil” OR “intubation” OR “supraglottic airway” OR “spinal anesthesia” OR “epidural” OR “regional anesthesia” OR “neuromuscular blocking drugs”. The search was done on 8 April, 2021. Inclusion criteria were all full-text articles about Rett syndrome and anesthesia in English. Due to the paucity of literature reporting on anesthesia for Rett syndrome, case reports were also included. Relevant papers that were identified in the reference list of included papers were also added.

A PRISMA flow chart showing the results is shown in figure 1.

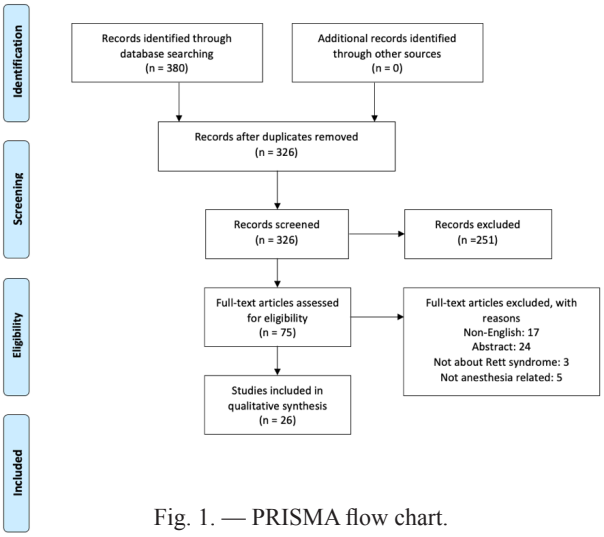


Fig. 1. — PRISMA flow chart.

## Results

### *Airway management*

Airway management in patients with Rett syndrome is reported to be potentially challenging due to limited mouth opening, micrognathia and limited cervical mobility (7).

Nho et al. described a case with difficult airway management due to limited mouth opening, requiring oral fiberoptic intubation (10). Motomura et al. described the use of a videolaryngoscope to intubate a patient with Rett syndrome with a mouth opening of 2 fingers (11). However, in a retrospective review by Karmaniolou et al. (12) out of 20 patients 80% had a Cormack-Lehane grade 1, 15% a grade 2 and one patient (5%) had a grade 3 with need of an endotracheal tube introducer (gum elastic bougie) (12).

### *Respiratory management*

A retrospective case-control series by Tofil et al. (9) compared adverse events during propofol sedation for lumbar puncture in patients with Rett syndrome versus control population. Patients with Rett syndrome experienced prolonged apnea in 33.3% of cases versus none in the control group despite receiving less propofol when adjusted for weight and duration of procedure (9). Rapid apnea resulting from induction with a volatile anesthetic (nitrous oxide and halothane) has been reported (13).

Similarly, one case report described an irregular breathing pattern after emergence from anesthesia with an episode of apnea requiring mask ventilation (14).

One of the earliest published case reports about anesthesia for Rett syndrome describes a prolonged recovery of anesthesia (15). Depth of anesthesia monitoring using bispectral index monitoring (BIS) might help in avoiding too profound levels of anesthesia (11, 13). However, one report was found that describes a delayed emergence despite using BIS (16).

One case was identified describing successful opioid-free anesthesia and analgesia for minor surgery (dental procedure) (17). Multiple cases were found describing anesthesia without major adverse events (13, 17, 18, 19, 20).

In murine models, long-term low-dose ketamine treatment ameliorates the symptoms of Rett syndrome (21). The NMDA-receptor might play an important role in the neurological regression typically observed in patients with Rett syndrome (21).

One study was identified where administration of midazolam resulted in the transient resolution of the characteristic breathing abnormalities in mice (22). In a small nuclear imaging study in humans, the binding of benzodiazepine to their receptor was found to be reduced in the cerebral cortex (23). These findings suggest that GABA-transmission might play an important role in the pathophysiology of Rett syndrome (22, 23).

### *Management and outcome during spinal fusion surgery*

A retrospective cohort study by Cohen et al. (24) compared different outcome measures patients with either cerebral palsy or Rett syndrome undergoing posterior spinal fusion surgery. Respiratory failure, intubation for more than 48h,

reintubation, positive pressure ventilation for more than 24h, duration of ICU stay, and incidence of pleural effusion were all significantly higher in the Rett group despite a significantly shorter duration of anesthesia and surgery and a better preoperative motor function (24). A similar retrospective cohort study by Rumbak et al. (25) found comparable results when comparing patients with Rett syndrome, neuromuscular scoliosis or idiopathic scoliosis undergoing scoliosis surgery. A longer ICU stay, more respiratory failure (all patients with Rett syndrome had respiratory failure), more days of mechanical ventilation and a longer length of stay was found in Rett syndrome (25). In this study patients with Rett syndrome had more intra-operative blood loss and transfusion of packed red blood cells, fresh frozen plasma, and blood platelets (25). A retrospective review by Karmaniolou et al. (12) found that the most common post-operative complications in patients with Rett syndrome after spinal fusion surgery were respiratory (pneumonia and need for continuous positive airway pressure) and gastrointestinal (feeding issues, vomiting & aspiration). The mean time that these patients were mechanically ventilated postoperatively was 4 days (12).

A retrospective study by Master et al. (26) found that somatosensory-evoked potentials (SSEP) can reliably be used in patients with Rett syndrome undergoing scoliosis surgery. The addition of transcranial motor-evoked potentials is controversial due to the high rate of epilepsy in Rett syndrome (26).

*Analgesic management*

Barney et al. (27) found in a case-controlled comparison that patients with Rett syndrome receive significantly lower doses of opioids after spinal fusion surgery when compared to patients with cerebral palsy, with comparable cognitive and motor function, and patients with idiopathic scoliosis. Observational pain assessment scores were similar between cerebral palsy patients and Rett syndrome patients despite the latter receiving significantly less opioids (27). A case report was also found reporting on markedly lower analgesic after spinal fusion surgery (28). Patients with Rett syndrome do have a higher level of beta-endorphin in their cerebrospinal fluid, leading to the hypothesis that the high level of endogenous opioids plays a role in the pathophysiology of Rett syndrome (29). In murine models, MECP2 plays a role in the regulation of the expression of the mu-opioid receptor and the nociceptor TrpV1 (transient receptor potential cation channel subfamily V member 1) (30). In other animal studies MECP2 is involved in central sensitization and the response of the amygdala to pain (30).

Different mutations of MECP2 exist in Rett syndrome, and result in different phenotypes with some mutations being more linked to decreased nociception (30).

Despite these findings, patients with Rett syndrome frequently do experience episodes of pain and chronic pain (31). The expression of pain might, however, vary significantly between individuals (30).

*Regional anesthesia and analgesia*

As already stated up to 75% of patients with Rett syndrome develop scoliosis (5), which may increase difficulty in the placement of neuraxial analgesia techniques. In one case, postoperative epidural analgesia containing bupivacaine (0.1%) and hydromorphone (20 µg/mL) had to be discontinued on the 2$^{nd}$ postoperative day due to mild desaturation caused by a decreased respiratory rate (32). Another case described using low dose intrathecal morphine (1µg/kg) as analgesic resulting in excellent analgesia but postoperative sedation without respiratory compromise was reported (33). In both these cases either the catheter or the injection was done by the surgeon during the spinal fusion surgery (32, 33). One case was found describing successful spinal anesthesia using bupivacaine and fentanyl for femur fracture surgery (34). The placement was difficult due to scoliosis and ketamine was administered for facilitating the placement of the spinal needle in an uncooperative patient (34). The further intra-operative and post-operative was uncomplicated, and no respiratory events were reported (34).

*Management of prolonged QT-interval*

Patients with Rett syndrome frequently have a prolongation of QTc interval and non-specific T wave changes (35). The cardiac autonomous nerve system is also affected in Rett syndrome with a reduced baroreflex and vagal tone. This leads to an increased sympathetic tone and might result in an increased risk of arrythmia and sudden death (35). One case described a sudden death four weeks after spinal surgery (36). Due to these risk factors, drugs that prolong QT-interval should be avoided in patients with Rett syndrome to potential malignant arrythmia (7, 35).

*Use of neuromuscular blocking drugs*

One case report was found describing a severe masseter spasm after the use of succinylcholine (37). In a case by Motomura et al. (11) sugammadex was successfully used to reverse a residual neuromuscular blockade by rocuronium.

## Discussion

Patients with Rett syndrome have risk factors for difficult intubation (limited mouth opening, micrognathia, and limited cervical mobility) (7). Two reports were identified where intubation was more difficult due to limited mouth opening (10) (11). In a retrospective review 5% of patients with Rett syndrome had a Cormack-Lehane score of 3 and difficult intubation conditions (12). This is higher than the general population where 1.2% has a Cormack-Lehane score during laryngoscopy (38). A Cormack-Lehane score of 3 is associated with difficult intubation (38). However due to the limited sample size (20 patients with 1 patient with Cormack-Lehane score of 3) (12) it is difficult to say whether higher Cormack-Lehane scores are more frequent in patients with Rett syndrome. The majority (80%) of patients with Rett syndrome had a Cormack-Lehane score of 1 (12), which is in strongly indicative for an easy intubation (38).

Patients with Rett syndrome are at an increased risk for prolonged apnea even when receiving sedation for minor interventions (9). Apnea can occur both during inhalation induction and emergence from anesthesia (13, 14). Major respiratory complications are significantly more frequent in patients with Rett syndrome undergoing spinal fusion surgery (12, 24, 25). This puts patients with Rett syndrome at risk for a longer mechanical ventilation time and a longer postoperative ICU stay (24, 25), even if the preoperative motor function is better preserved than the non-Rett population (24).

Patients with Rett syndrome seem to have lower opioid requirements to reach adequate analgesia (27). Since different MECP2 mutations result in different nociceptive phenotypes (30), nociception might differ considerably between patients with Rett syndrome. Whether the decreased analgesic requirement is due to increased sensitivity to opioids, decreased pain sensitivity or the failure to assess pain correctly in this nonverbal population is unclear. Neuraxial anesthesia is possible in Rett syndrome despite scoliosis (34). The addition of opioids to epidural or intrathecal administered local anesthetics can result in respiratory depression or prolonged sedation (32, 33). This illustrates the increased susceptibility of patients with Rett syndrome for adverse effects of opioids. Remifentanil can be considered due to its short duration of action (7), but no trials are available to corroborate this.

QT-prolonging drugs should be avoided due to frequent long QT-interval in patients with Rett syndrome (7, 35).

Succinylcholine is contra-indicated in different types of neuromuscular disease (motor neuron diseases, muscular dystrophies & myopathies) due to risk of malignant hyperthermia, rhabdomyolysis, hyperkalemia and cardiac arrest, depending on the type of neuromuscular disease (39). No cases were identified for Rett syndrome describing these complications. However, 50% of patients with Rett syndrome will become non-ambulant in the course of the syndrome (8) and immobilization can make patients prone to developing hyperkalemia after administration of succinylcholine (40). Succinylcholine is also not a good choice in patients with prolonged QT due to its autonomic effect (41). Succinylcholine is not recommended in Rett syndrome due to QT-elongation caused by its autonomic effect and due to possible hyperkalemia (7). Reversing neuromuscular blockade with a cholinesterase inhibitor (neostigmine or edrophonium) in combination with an anticholinergic drug (atropine or glycopyrronium) is also not recommended in patients with prolonged QT due to QT-elongation (42). Sugammadex, however, has negligible effect on the QT interval (43) and therefore seems the ideal agent for reversing rocuronium induced neuromuscular blockade in patients with Rett syndrome.

## Conclusion

Optimal anesthesia management of patients with Rett syndrome requires attention to specific aspects of this syndrome. There are risk factors for difficult airway management (7), but a difficult airway is probably present in only a minority of cases (12). Most patients with Rett syndrome (75%) develop scoliosis (5), which may require spinal fusion surgery. Patients with Rett syndrome are more likely to have respiratory complications after spinal fusion surgery (12, 24, 25) and have a longer mechanical ventilation time and longer postoperative ICU stay (24, 25). Major respiratory events can occur even when undergoing minor procedures (9). Differences in nociception might exist in patients with Rett syndrome (30) resulting in some patients

with decreased analgesic requirements (27). The high incidence of scoliosis can complicate the use of neuraxial anesthetic techniques, but its use has been reported (34). Patients with Rett syndrome seem to have increased sensitivity to side effects of opioids, even when administered epidurally or intrathecally (32, 33).

QT-prolonging drugs should be avoided due to frequent long QT-interval in patients with Rett syndrome (7, 35). Succinylcholine is not recommended in Rett syndrome due to its QT-elongating effect (41) and risk of hyperkalemia in immobilized patients (40). The use of a cholinesterase inhibitor and an anticholinergic drug for reversal of neuromuscular blockade is also not recommended due to its QT-elongating effect (42). Sugammadex, due to its negligible effect on QT-interval (43), should be considered when reversal of neuromuscular blockade by rocuronium is indicated.

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