Aquaporin 4 expression in the hippocampus in sudden infant death syndrome and sudden unexplained death in childhood

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A B S T R A C T

Aquaporin 4 (AQP4) is the main membrane water channel in the brain involved in regulating water homeostasis. The water distribution in neural tissue is often dysregulated after hypoxic neural injury. Previous research has indicated that victims of sudden infant death syndrome (SIDS) and sudden unexplained death in childhood (SUDC) have an underlying brain dysfunction that impairs their critical arousal response to hypoxic stress during sleep. The aim of this study was to determine the expression levels of AQP4 in the hippocampus in SIDS/SUDC cases and controls, and compare the findings with AQP4 genotypes that previously have been shown to be associated with SIDS. Immunohistochemical staining and morphometry were used to evaluate the density of AQP4-positive astrocytes in 30 SIDS/SUDC cases and 26 controls. AQP4-positive cells were counted in grids covering three layers in the hippocampus, which revealed that their count in any of the layers did not differ significantly between cases and controls. A decline in AQP4 expression was observed for infants older than 12 weeks. The AQP4 expression was lower in infants and children with the rs2075575 CT/TT genotype than in those with the CC genotype. This study indicates that AQP4 expression may be influenced by both age and genotype in infants. The role of AQP4 in the pathogenesis of SIDS remains to be elucidated.

1. Introduction

Sudden infant death syndrome (SIDS) and sudden unexplained death in childhood (SUDC) are defined as the sudden unexpected death of infants aged <1 year and of children >1 year, respectively. The onset of the fatal episode apparently occurs during sleep, and the death remains unexplained after a thorough investigation, including performing a complete autopsy and reviewing the circumstances of the death as well as the clinical history (Krous et al., 2004; Krous et al., 2005).

There is evidence that disturbance in the development and regulation of brain function is involved in SIDS (Bright et al., 2018), perhaps involving abnormalities in a network of neural pathways controlling critical homeostatic mechanisms. One important region is the brain stem, where developmental abnormality may lead to dysfunction of the serotonergic network and the failure of protective mechanisms against hypoxia (Kinney and Haynes, 2019). This theory is supported by findings of elevated levels of hypoxic markers in SIDS (Rognum and Saugstad, 1991; Opdal et al., 1995; Jones et al., 2003).

The hippocampus has become a focus of SIDS and SUDC research (Kinney et al., 2016; Kinney et al., 2015; Waters et al., 1999; Rodriguez et al., 2012; Kinney et al., 2009; Kinney et al., 2018). The high energy metabolism of the hippocampus makes it the first cerebral organ to be affected by anoxic conditions (Chimelli and Gray, 2014). Neuronal apoptosis in hypoxia-sensitive subregions of the hippocampus as well as hippocampal abnormalities similar to lesions associated with temporal lobe epilepsy have been reported in some SIDS/SUDC cases (Kinney et al., 2016; Kinney et al., 2015; Waters et al., 1999).

Aquaporin 4 (AQP4) is the main water channel in the brain, and is highly expressed in the perivascular domains of astrocytes and the subpial domains of ependymal cells, where it is involved in water transmembrane transport. Dysregulation of AQP4 expression has been associated with neurological disorders such as multiple sclerosis, multiple sclerosis-like disease, and Alzheimer’s disease (Nishida et al., 2013; Ito et al., 2014; Kwon et al., 2015). AQP4 expression was lower in infants and children with the rs2075575 CT/TT genotype than in those with the CC genotype. This study indicates that AQP4 expression may be influenced by both age and genotype in infants. The role of AQP4 in the pathogenesis of SIDS remains to be elucidated.

**Abbreviations**: AQP4, aquaporin 4; CA, cornu ammonis; SIDS, sudden infant death syndrome; SNP, single-nucleotide polymorphism; SUDC, sudden unexplained death in childhood.

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exchange between the brain tissue, bloodstream, and cerebrospinal fluid (Nielsen et al., 1997). The water distribution in neural tissue is often dysregulated after hypoxic neural injury and neurotrauma (Stokum et al., 2016). AQP4 plays a significant role in the development of brain edema, and AQP4-/- mice show less brain swelling, improved neurologic outcomes, and higher survival rates after middle cerebral artery occlusion and water intoxication compared with wild-type mice (Manley et al., 2000).

Both loss-of-function and gain-of-function polymorphisms have been identified in the AQP4 gene (Sorani et al., 2008a; Sorani et al., 2008b). A study of the AQP4 gene in Norwegian SIDS cases and controls disclosed an association between rs2075575 CT/TT and SIDS (Opdal et al., 2010). A further association was found between rs2075575 CT/TT and a higher brain/body weight ratio in SIDS infants aged 0.3–12 weeks (Opdal et al., 2010), suggesting that genotypes containing the T allele contribute to the development of brain edema in young children and infants.

Because the hippocampus has become an interesting brain region in SIDS research, the aim of this study was to determine the distribution of AQP4-positive astrocytes in the hippocampus of SIDS cases and controls, and also to examine relationships of hippocampal AQP4 expression with the AQP4 rs2075575 genotype.

2. Materials and methods

2.1. Subjects

The subjects in this study consisted of 26 SIDS cases, 4 SUDC cases, and 26 controls (Table 1). Both the cases and controls had been autopsied at the Department of Forensic Sciences, Oslo University Hospital during the period 1988–2015.

The SIDS and SUDC cases were classified according to the San Diego definition, applying the criteria used in the Nordic SIDS study (Krous et al., 2004; Gregersen et al., 1995). The investigation protocol included evaluating the circumstances of death, reviewing the medical and family history, and performing a total skeletal radiographic examination and a thorough autopsy with extensive histologic, microbiologic, toxicologic, and neuropathologic examinations. None of the cases had mutations in genes related to long-QT syndrome or the ACADM gene (which causes MCAD deficiency). Information on age, prematurity, sex, cause of death, and circumstances of death were obtained from the autopsy journals (Table 1). All except one of the patients were Caucasians from the southeastern part of Norway.

2.2. Genotyping

DNA was extracted from the spleen using the QiAmp DNA minikit and the BioRobotEZ purification system (Qiagen, Hombrechtikon, Switzerland). The single-nucleotide polymorphism (SNP) rs2075575 was genotyped using the TaqMan SNP genotyping assay (Applied Biosystems, Foster City, CA, USA) and a real-time PCR device (ABI 7500 Thermo Fisher Scientific, Waltham, MA, USA) according to manufacturers’ instructions. The genotypes of 19 of the SIDS cases have been published previously (Opdal et al., 2010).

2.3. Tissue preparation and immunohistochemical staining

The brains were obtained at the autopsy and fixed in 10% formaldehyde for at least 4 weeks before being examined. Tissue specimens from the anterior hippocampus (in line with the lateral geniculate nucleus) were obtained thereafter, and further fixed in 4% formaldehyde until processing and paraffin embedding. The tissue blocks were serially sectioned using a microtome at 4 μm and mounted on Polylysine-coated slides (Thermo Fisher Scientific). Antigen reactivity was retrieved using heat-induced epitope retrieval with a citrate buffer (pH 6).

The primary antibodies applied were anti-AQP4 at a dilution of 1:12,500, made in rabbit (HPA014784, lot B91956, Sigma-Aldrich, St. Louis, MO, USA), and anti-GFAP at a dilution of 1:10,000, made in mouse (no. 131 17719, lot 1819891, Invitrogen by Thermo Fisher Scientific).

After 30 min of incubation at 20 °C with the primary antibody, the AQP4-stained sections were incubated with the secondary antibody using the ImmPRESS™ HRP Anti-Rabbit IgG (Peroxidase) Polymer Detection Kit (MP-7401, Vector Laboratories, Burlingame, CA, USA) and visualized using the ImmPACT DAB Peroxidase (HRP) Substrate (SK-4105, Vector Laboratories). The substrate was incubated for exactly 10 min at room temperature, with immunoreactivity appearing brown.

The adjacent section was stained with anti-GFAP using a similar procedure except for using the secondary antibody ImmPRESS-AP Anti-Mouse IgG (Alkaline Phosphatase) Polymer Detection Kit (MP-5402, Vector Laboratories) and the ImmPACT Vector Red Alkaline Phosphatase Substrate (SK-5105, Vector Laboratories). The substrate was incubated for exactly 20 min in room temperature, with immunoreactivity appearing red.

The tissue sections were dehydrated, counterstained with hematoxylin, and mounted. Negative controls were treated identically except with the omission of primary antibodies.

2.4. Morphometric analysis

AQP4-positive astrocytes were quantified under a Leica microscope with a 40× objective and a 10× ocular equipped with a grid. The grid area was 0.04 mm², and so a count of 10 positive cells per grid equaled 250 positive cells/mm². The following three layers of the hippocampus were quantified separately (see Fig. 1A): (1) the alveus/stratum oriens region, (2) the stratum pyramidale, and (3) the stratum radiatum/lacunosum/molecular area. On average there were 30, 20, and 15 grids counted in the first, second, and third (inner) layers, respectively. Cells exhibiting positive immunostaining in a star-shaped pattern similar to

| Group | Number of cases | Cause of death | Sex (male/ female) | Age, weeks | Corrected age, weeks | Postmortem time, hours |
|-------|----------------|----------------|-------------------|------------|----------------------|------------------------|
| SIDS  | 26             | SIDS           | 17/9              | 19.25      | 17.25                | 27                     |
|       |                |                |                   | (2.43.5)   | (.4-4.3.5)            | (3.5-1.07)             |
| SUDC  | 4              | SUDC           | 2/2               | 66.85      | 66.85                | 15.8                   |
|       |                |                |                   | (53.7-117.9)| (53.7-117.9)         | (15-1.6.6)             |
| Infant controls (≤52 weeks) | 9 | 5 asphyxia (suffocation/drowning) | 5/4 | 26 | 26 | 20.3 |
|       |                |                |                   | (4.4-4.2.7)| (4.4-4.2.7)          | (16.8-62.8)            |
| Child controls (>52 weeks) | 17 | 15 asphyxia (suffocation/drowning) | 8/9 | 127 | 127 | 23.3 |
|       |                |                |                   | (53.4-197.1)| (53.4-197.1)         | (12.5-1.44)            |

* median (range).
the shape of astrocytes were counted (Fig. 1B). In some cases the cells that were stained positive for AQP4 could be verified as GFAP-positive astrocytes in adjacent sections.

2.5. Reproducibility

To test the reproducibility of the counting system, 14 sections were examined by two different observers (J.M.L.E. and T.O.R.), and then the main observer (J.M.L.E.) re-examined the sections after 8 weeks.

2.6. Statistics

Intra- and interindividual reproducibility was assessed using Cohen’s kappa ($\kappa$) test. Mean AQP4 counts were calculated according to diagnosis, genotype and age using the Kruskal-Wallis test for more than two groups, and the Wilcoxon or Mann-Whitney $U$ test when comparing exactly two groups. All statistical analyses were performed using IBM SPSS Statistics (version 25.0, SPSS, Chicago, IL, USA).

3. Results

3.1. Reproducibility

There was substantial intra- and interindividual reproducibility in the quantification of AQP4-positive astrocytes ($\kappa = 0.745$ and 0.759, respectively).

3.2. Determination of AQP4 expression

The density of AQP4-positive astrocytes varied considerably within each layer of the hippocampi investigated, and so the total length of each of layer 1–3 was counted. In layers 1 and 2, the number of grids was sufficient to obtain a stable mean cell count, while in layer 3 the area was too small to obtain stable mean values.

Both the left and right hippocampi were available for analysis in 29 cases. In each of these cases the AQP4 expression was determined in both hippocampi, and the mean count for the case was calculated for each layer. This value was used in the subsequent statistical analyses.

The average AQP4-positive astrocyte count for each of the 56 cases and controls was calculated as the mean count across all three layers. The AQP4-positive astrocyte count for each of the included subjects is given in supplementary material, table S1.

3.3. Comparison between SIDS/SUDC and controls

The mean AQP4-positive astrocyte count for any of the three layers did not differ significantly between the SIDS/SUDC cases and controls (Table 2). This was also the case when investigating SIDS vs infant controls ($p = 0.926$, $p = 0.725$, and $p = 0.838$ for layers 1–3, respectively, and $p = 0.725$ for all three layers combined) and SUDC vs child controls ($p = 0.517$, $p = 0.574$, and 0.897, respectively and $p = 0.574$ for all three layers combined).

3.4. Density of AQP4-positive astrocytes according to genotype

The AQP4-positive astrocyte count differed significantly with the AQP4 rs2075575 genotype (Fig. 2), being lower in the CT/TT than the CC genotype in layer 3 when investigating the layers separately as well as when considering all three layers combined ($p = 0.015$ and 0.025, respectively).

3.5. Density of AQP4-positive astrocytes, age and sex

The AQP4-positive astrocyte count differed significantly with age (Table 3), being higher for infants $\leq 12$ weeks of corrected age than for ages of 12.1–52 weeks ($p = 0.022$) and $> 52$ weeks ($p = 0.014$). The three premature neonates with corrected age $< 0$ weeks all had very high AQP4-positive astrocyte counts (median 7.9, range 7.8–12.6). No association was observed between AQP4 astrocyte expression and sex.

Table 2

| Number of cases | Layer 1 | Layer 2 | Layer 3 | Average across all layers |
|-----------------|---------|---------|---------|--------------------------|
| SIDS/ Controls  | 30      | 3.94    | 5.15    | 4.64                     |
| Controls        | 26      | 2.88    | 5.10    | 3.97                     |
| p-value         | 0.324   | 0.25    | 0.755   | 0.421                    |

* median (range) given as count per grid.

a Mann-Whitney U test.
Fig. 2. AQP4-positive astrocyte counts separately in the three layers and the average across all three layers. Black lines indicate median values. The AQP4-positive astrocyte count was lower in cases/controls with the CT/TT genotype than the CC genotype in layer 3 ($p = 0.015$) and across all layers ($p = 0.025$).

Table 3
Average AQP4-positive astrocyte count according to age.

| Age group  | Number of cases | Average AQP4 count | p-value, compared with age group ≤ 12 weeks |
|------------|-----------------|--------------------|------------------------------------------|
| ≤ 12 weeks | 11              | 5.71 (1.8-12.6)    | 0.022                                    |
| 12.1-52 weeks | 24              | 3.70 (1.3-7.1)    |                                          |
| >52 weeks  | 21              | 4.14 (2.2-8.1)    | 0.014                                    |

* Corrected age.
\textsuperscript{b} median (range) given as count per grid.
\textsuperscript{c} Mann-Whitney U test.

4. Discussion

The main finding of this study is that the AQP4 rs2075575 CT/TT genotype is associated with a low density of AQP4-positive astrocytes in the hippocampus, both for the inner of the three counted layers as well as for the average density across the hippocampus. It was further found that the average AQP4-positive astrocyte density was highest in the youngest age group (≤ 12 weeks, corrected age). This is particularly interesting since it is known that the brains of the youngest infants have the highest water content (Bastiani et al., 2019; Pannek et al., 2012). Together with our previous finding that the CT/TT genotype is associated with a higher brain/body weight ratio in the youngest SIDS victims (Opdal et al., 2010), the present study strengthens the hypothesis of dysregulation of water homeostasis in the brain of SIDS patients. Associations between AQP4 expression and neurologic disorders have been established previously (Papadopoulos and Verkman, 2013), and the rs2075575 CT/TT genotype has been reported to be associated with leukoaraiosis, neurormelitits optica, and SIDS (Opdal et al., 2010; Ogasawara et al., 2016; Yadav et al., 2014). In addition to the association between the CT/TT genotype and SIDS infants aged 0.3–12 weeks with a high brain/body weight ratio (Opdal et al., 2010), associations between a combination of the CC genotype in rs17375748, rs1130183, rs12133079, and rs1186608 (4xCC) in the gene encoding Kir4.1 and SIDS have also been reported (Opdal et al., 2017). Kir4.1 is a potassium channel that is coexpressed with AQP4, and alterations in the expression of the AQP4–Kir4.1 complex can disrupt water and ion homeostasis, which in turn may influence brain development. Previous studies have revealed focal bilamination of granule cells and other developmental abnormalities in the dentate gyrus of the hippocampus in about 40% of SIDS cases (Kinney et al., 2015). Hippocampal disorganization may lead to a cardiorespiratory instability before the clinical onset of seizures and death in a predisposed infant. Schiering et al. (2014) found an association between increased AQP4 expression and prominent edematous cell changes (so-called diffuse edema) throughout the hippocampus after perinatal asphyxia in a study including three SIDS infants. They confirmed alterations in the blood–brain barrier by detecting the leakage of albumin uptake in astrocytes, and also found that these alterations were correlated with the presence of seizures. Together with the findings of the present study, this further emphasizes the possibility of hippocampal dysfunction in sudden unexpected infant death.

The hypothesis of an association between hypoxic/ischemic injury in the hippocampus and SIDS was investigated by Oehmichen et al. (2009). They found that the number of microtubule-associated protein reactive neurons was smaller in SIDS cases than in controls without hypoxic/ischemic injury, while there was no difference between SIDS and control infants with hypoxia/ischemia. That study clearly demonstrates the importance of selecting appropriate control groups when studying SIDS, and may explain the lack of differences in AQP4 counts found between SIDS/SUDC cases and controls in the present study, since most of the controls were due to asphyxia.

The hippocampus is commonly divided into the following four subfields of the cornu ammonis (CA): CA1, CA2, CA3, and CA4. In our series of cases, the overall variation in AQP4 expression appeared to be most prominent in what we called layer 3, containing the stratum radiatum/lacunosum/moleculare along the hippocampal fissure. Laminar-specific AQP4 expression in the hippocampus—with more intense immunoreactivity in this particular area—has been seen in rats, especially in the CA1 region (Hubbard et al., 2015). This region corresponds to the anatomically defined Sommer’s section, and is often the field most affected by hypoxia (Chimelli and Gray, 2014). In the present study we were not able to distinguish between different CA layers, but the inner layer of CA1 was where we observed the largest variations between cases.
AQP4 expression in the brain increases from the early gestational age throughout the pregnancy and into the first weeks of the postnatal period (Wen et al., 1999; El-Khoury et al., 2006; Hsu et al., 2011). Rat studies have found that AQP4 levels in the hippocampus and cerebellum are highest when the rat brain is considered mature (Wen et al., 1999; Hsu et al., 2011). El-Khoury et al. (2006) investigated developing infants, and found that the perivascular coverage of AQP4 increased steadily from gestational ages of 19–40 weeks (El-Khoury et al., 2006). Our data suggest that the expression of AQP4 decreases as the infant passes the first 12 weeks of life (Table 3). Indeed, the highest density of AQP4 expression was observed among the youngest infants born premature. It thus seems that in human brains, AQP4 expression peaks at birth and then decreases during the first months of life.

The model of a fatal triangle (also called a triple-risk model) in SIDS is well established (Rognum and Saugstad, 1993; Gunteroth and Spiers, 2002). This model posits that SIDS/SUDC is a consequence of the interplay between a vulnerable developmental period in the central nervous system, environmental risk factors, and a genetic predisposition (Rognum and Saugstad, 1993). The findings of the present study of hippocampal AQP4 expression being associated with both the AQP4 rs2075575 genotype and age shed further light on the vulnerability of the central nervous system during the first months of life.

There were no significant differences in AQP4-positive astrocyte count when comparing SIDS vs. infant controls and SUDC vs child controls, respectively, nor were there any significant differences when these were pooled into SIDS/SUDC vs. infant/child controls (Table 2). The differences between SIDS and SUDC are first and foremost the age spectra, with SIDS happening in week 2–52 of life and SUDC in the age range 1–3 years (Krous et al., 2005). SUDC is further characterized by being predominantly male, and frequently having a personal and family history of seizures that are often associated with fever (Krous et al., 2005). The SUDC cases included in the present study all had a history of seizures or epilepsy in the family. Since SIDS and epilepsy have shown similarities in death mechanism and similar epileptogenic patterns in the hippocampi (Kinney et al., 2015) these were put in the same group, SIDS/SUDC.

This study was subject to a few limitations. The lack of standardized neuropathologic procedures may have resulted in the samples being collected from different areas of the hippocampus. There were also slight variations in the postmortem time, which may have impacted the quality of the tissue sections. Incomplete information on seizures in the clinical history limited our ability to interpret the results further with regard to febrile convulsions or epilepsy. Furthermore, due to the limited sample size, especially in the SUDC group, these data should be considered preliminary. Further research is needed in order to confirm our findings.

5. Conclusion

This study shows that AQP4 expression in the hippocampus is lower in infants with the rs2075575 CT/TT genotype than the CC genotype, and higher in the youngest infants (<12 weeks). Based on the high water content of brains of the youngest infants and our previous finding of an association between the CT/TT genotype and the brain/body weight ratio in SIDS infants younger than 12 weeks, the present results strengthen the hypothesis that the rs2075575 CT/TT genotype represents a genetic risk factor for a subgroup of SIDS patients. One possible underlying mechanism is an increased risk of subclinical seizures and a decreased ability to eliminate hypoxia-generated edema fluid.

Author contributions

J.M.L. Eidahl: Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Visualization. A. Stray-Pedersen: Formal analysis, Validation, Writing - Review & Editing, Visualization. T.O. Rognum: Methodology, Conceptualization, Validation, Writing - Review & Editing, Supervision, Funding acquisition. S.H. Opdal: Validation, Formal analysis, Resources, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

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Ethics

This research project was approved by the Norwegian Regional Committee for Medical and Health Research Ethics. The right to access confidential information from the autopsy journals was granted by the Regional Public Prosecution Office in Oslo.

All next of kin were given the opportunity to register in a non-research exclusion register, and were explicitly informed that they could withdraw their deceased from this research study at any time.

The study was reviewed and approved by the National Committees for Research Ethics in Norway.

Declaration of Competing Interest

There were no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jchemneu.2021.101962.

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