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**Conditions requiring hospitalisations, more than general anaesthesia itself, are associated
with diagnosis of learning disorders in children**

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Abstract

Background

Anaesthesia is neurotoxic in developing primates. Retrospective clinical studies show a correlation between exposure to anaesthesia during infancy and the occurrence of learning disorders (LD). Prospective studies failed to detect any influence of a single exposure to anaesthesia on neurodevelopment. We hypothesised that some specific populations of children were electively sensitive to anaesthesia-related neurotoxicity.

Methods

Using a case-control design, we analysed the medical histories of children with LD, compared to those of their normally reading siblings. Interviews were conducted and medical records were reviewed. The numbers of hospitalisations and anaesthesia exposures before the age of five years were determined.

Results

Four hundred fourteen dyslexic children were screened over a one-year period. Two hundred and seventy patients were excluded due to confounding variables (single child, all siblings showing LD or any condition placing the neurological prognosis at risk (N = 107/414 for the latter)) or inability to accurately collect evaluation criteria. In the 144 case-control pairs studied, the mean number of hospitalisations was significantly different (N = 1.097 ± 0.135 /case *versus* 0.667 ± 0.097 /control, $p = 0.0052$), as was the proportion of hospitalised patients (54.2% *versus* 38.9%, $p = 0.0031$). The mean number of anaesthesia exposures per individual was not statistically different (N = 0.958 ± 0.183 /case *versus* $0.569 \pm$

0.107/control, $p = 0.0732$), but the proportion of children anaesthetised at least once was (43.8% (cases) *versus* 33.3% (controls), $p = 0.0301$).

Discussion

One or more hospitalisation(s) may reflect a health status and/or have an iatrogenic effect disrupting the normal setting up of learning abilities. Anaesthesia may play a role, but a correlation between LD and anaesthesia is of a lower magnitude than between LD and hospitalisation.

Keywords:

Anaesthesia – Brain development – Dyslexia – Learning disorders – Neurotoxicity

Abbreviations

CNS: Central Nervous System

LD: Learning Disorder(s)

SPC: Socio-professional category

1. Introduction

Experimental studies have shown that exposure to anaesthetic drugs is neurotoxic in developing mammals, including primates, yielding long lasting cognitive and behavioural defects in the latter [1,2]. This can be related to several mechanisms, among which a decrease in the expression of some neurotrophic factors [3], the mobilisation of calcium by the endoplasmic reticulum inositol triphosphate receptors and the subsequent induction of neuroapoptosis [4].

In humans, retrospective cohort studies have shown conflicting results, some studies showing a correlation between the number of exposures to general anaesthetics during pregnancy or infancy and the diagnosis of learning disorders (LD) [5-10] (a group of developmental disabilities that prevent normal speech, reading and writing [11]), while others provided negative results [12]. Again, recently, Khochfe et al. observed that exposure to general anaesthesia before the age of two years was associated with an increase in the frequency of the attention – deficit with hyperactivity disorder (ADHD), a disorder that falls within the framework of learning disorders [13, 14].

On the other hand, two large recent studies, namely the GAS trial (General Anaesthesia *versus* Spinal, randomised controlled trial) [15] and the PANDA (Pediatric Anesthesia NeuroDevelopment Assessment) study (ambidirectional, cohort study) [16] failed to establish a specific link between early, single, brief exposure to general anaesthesia when compared to spinal anaesthesia [15] or with no anaesthesia [16] in infancy, regarding the occurrence of subsequent cognitive impairment.

Another large ambidirectional study, the Mayo Anesthesia Safety in Kids (MASK) study, did not find any relationship between a single exposure to anaesthesia before the age of three

years and a subsequent alteration of global intelligence in children, but found that multiple exposures were associated with behavioural and learning difficulties [17]. Notably, the GAS, PANDA and MASK studies analysed subjects from the general population, but were unable to conclude whether some specific subgroups of children were more prone to difficulties following surgical or diagnosis procedures under general anaesthesia. Also, beyond the question of a simple relation between anaesthesia and neurocognitive issues, one must consider the putative role of the disease as well as that of hospitalisation, the latter meaning abrupt separation from the normal environment.

Taken together, a body of variables related to surgical conditions in infancy could theoretically influence the normal setting up of cognitive and language skills in young children, maybe even more so in some specific populations. Moreover, already known environmental factors related to the occurrence of behavioural abnormalities, like socio-economic status, are likely to represent risk factors which could be somewhat controlled by studying the same familial environment [18]. In conclusion, the high number of confounding variables likely to interfere with a possible neurotoxic effect of general anaesthetics makes further analysis mandatory [19].

2. Material and Methods

The ANNTA study (Anesthésie du Nouveau-né, du Nourrisson et Troubles des Apprentissages) used a case-control design. Its protocol followed all rules in ethics according to French law [20] and was approved by the local Institutional Review Board prior to any research activity (decision made on December 15, 2016).

2.1. Objective and aim of the study

The study objective was to record the number of hospitalisations and anaesthesia exposures before the age of five years (an age at which children begin to read) in children with developmental LD (cases) and their normally reading siblings (controls), raised in the same familial environment and socio-economic conditions.

The aim of the study was to show a higher number of hospitalisations and anaesthesia exposures per individual before the age of five years in cases when compared to controls (normally reading siblings).

2.2. Study protocol

The study was conducted in the reference center for language and learning disorders of a tertiary care university hospital, from March 1, 2017 to February 28, 2018. During this period, the parents of all children consulting for oral and/or written language disorders and/or attention deficit/hyperactivity disorders were interviewed after their routine consultation.

2.2.1. Inclusion criteria

Cases were defined as children with LD i.e. dyslexia, dysgraphia, dyscalculia, dyspraxia (coordination disorder) and/or attention deficit/hyperactivity disorders, all disorders characterised by the inability to appropriately process printing, resulting in an inappropriate setting for reading and writing. Diagnostic criteria for LD were in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), fifth edition [14]. The completeness of the cohort was controlled by cross-checking with the hospital's Medical Information Systems database.

2.2.2. Exclusion criteria

Children were excluded for the following reasons (see also Figure 1, flow chart): parents refusal, no available control (all siblings showing LD, adopted child or single child, unique sibling aged less than five years), inability to accurately collect evaluation criteria, all conditions placing the neurological or developmental prognosis at risk, namely any central nervous system (CNS) injury or situation at risk of CNS injury (prematurity, intrauterine growth retardation, perinatal anoxia, perinatal brain trauma, stroke, cerebral haemorrhage, epilepsy, febrile seizures, head trauma, CNS infection, other developmental disorder (autism), any kind of brain tumour, any genetic syndrome, foetal alcohol or teratogenic drug exposure, cerebellar ataxia, corpus callosum agenesis), any condition affecting the sensory prognosis (ocular or hearing impairment).

2.2.3. Interviews with parents

After receiving oral information on the rationale and purposes of the work, written informed consent was obtained from the parents of all patients except four, who were not included in the study. Parents were then interviewed regarding the medical history of their children. More precisely, all data on complications occurring during pregnancy or at birth and likely to have an influence on the development of the child; data on hospitalisation, anaesthesia exposures, surgery, invasive procedures or critical conditions were collected, as well as the hospital where care was provided. In addition to the interviews, medical charts were reviewed.

2.2.4. Selection of controls

Parents were asked for the same data for all siblings. One case was compared to one control. Controls were a brother or sister of the case, closest in age, always aged more than five years, without LD.

2.2.5. Evaluation criteria

For each individual, case or control, the numbers of hospitalisations and anaesthesia exposures were recorded. Each anaesthesia exposure, including outpatient procedures, was considered as giving rise to a hospitalisation.

2.2.6. Subgroup analysis

First, in order to take the complexity of the procedure into account, since different types of surgeries were performed, we categorised surgeries in two groups, simple (e.g. tonsillectomy) or complex procedures (e.g. thoracotomy) based on experts' opinion taking

into account the anticipated length of stay in hospital (see Table 3, supplemental data). We analysed the putative difference of distribution between simple and complex surgery in cases and controls.

Second, we compared case-control pairs of infants that experienced hospitalisation but not anaesthesia to case-control pairs of infants having been exposed to both.

Third, since LD are a group of conditions with a parental component and socio-professional aspects (LD are known to be more frequent in low socio-professional categories [18]), the highest socio-professional category (SPC) of the parents (or single parent) was collected. This was done in order to control for a putative influence of the socio-familial environment on the presence of LD. Case-control pairs were classified in SPCs according to parents' level of education (six levels) in accordance with INSEE criteria (<https://www.insee.fr/fr/metadonnees/definition/c1076>). As the number of pairs in each category was low, we distributed them in two groups of SPC: SPC⁻ and SPC⁺. The comparison of numbers of hospitalisations and anaesthesia exposures was done in the whole sample and separately in SPC⁺ and SPC⁻ subgroups.

2.3. Statistical analysis

The number of hospitalisations and of anaesthesia exposures per child before the age of five years in the group of children with LD and in paired controls were compared using paired parametric (paired two-tailed t test) statistics.

The total numbers of children hospitalised at least once and anaesthetised at least once, before the age of five years in cases and controls, respectively, were compared using Fisher's exact test.

The total numbers of cases and controls anaesthetised at least once were compared for all surgical procedures, on the one hand, and for only simple surgical procedures, on the other hand, using Fisher's exact test.

Odds ratios (ORs) for hospitalisation or anaesthesia in cases *versus* controls and 95% confidence intervals were calculated. Distribution of cases and controls in three subgroups ((i) non-hospitalised, ii) hospitalised at least once but not anaesthetised and iii) hospitalised at least once and anaesthetised at least once) was analysed by Chi square test.

Whether more children with LD had been hospitalised than controls was examined separately in SPC⁺ and SPC⁻ families using two-tailed Fisher's exact test.

The number of children to be recruited was calculated as follows: considering a hypothesis of a ratio of the number of hospitalisations/anaesthesia exposures between cases and controls of 2, with one case per control, 30% of controls exposed to hospitalisation/anaesthesia and a power of 80%, 133 case/control pairs had to be recruited.

A *P* value less than 0.05 was considered significant. Statistics were run using Prism software (GraphPad, San Diego, CA, USA).

3. Results

Four hundred and fourteen children were screened. Two-hundred and seventy were excluded (see figure 1). One hundred and forty-four case-control pairs were studied. Reasons for hospitalisation are listed in table 1. Diagnostic categories justifying anaesthesia are listed in table 2.

Among the 144 case-control pairs, there were 116 boys and 28 girls in cases and 61 boys and 83 girls in controls, a consistent result with the reported sex-ratio in children with LD [14].

3.1. Hospitalisation

The number of hospitalisations per child before five years of age was significantly higher in cases when compared to their respective normally reading controls ($1.097 \pm 0.135/\text{case}$ vs $0.667 \pm 0.097/\text{control}$, mean \pm SEM, $p = 0.0052$) (figure 2). Of 144 case-control pairs, seventy-nine cases (54.2%) were hospitalised at least once before the age of five years *versus* 57 controls (38.9%) ($p = 0.0031$ in two-tailed Fisher's exact test, OR for hospitalisation case *versus* control 1.857 (CI₉₅ 1.162 - 2.968)) (figure 3A). The majority of hospitalisations were related to infectious conditions (see table 1).

3.2. Procedures requiring anaesthesia

The number of procedures requiring anaesthesia per child before five years of age was not significantly different between cases and controls ($0.958 \pm 0.183/\text{case}$ vs $0.569 \pm 0.107/\text{control}$, mean \pm SEM, $p = 0.0732$) (figure 2). Sixty-three cases (43.8%) were anaesthetised at least once before the age of five years *versus* 48 controls (33.3%; $p = 0.0301$, Fisher's exact test; OR for anaesthesia case *vs* control 1.556 (95CI 0.9644 - 2.509)) (figure 3B). Types of procedures requiring anaesthesia are listed in table 2. Only one child was operated when newborn (i.e. before 28 days of life) and was the only child operated under regional anaesthesia alone.

3.3. Effect of the type of surgery

Surgical procedures were categorised as "simple" and "complex", as presented above (see section 2.2.6. and Table 3 (supplemental data)). When comparing distributions of absolute numbers of anaesthetised *versus* non-anaesthetised cases and controls for all surgeries

(figure 3B) and for only simple surgeries (figure 3C), we show that distributions were significantly different when comparing all surgeries ($p = 0.0301$), but not when comparing simple surgeries only, according to Fisher's exact test ($p = 0.0868$).

3.4. Effect of socio-professional background

Eight families could not be classified. Seventy-five case-control pairs were classified into high (SPC⁺) and 61 pairs into low (SPC⁻) socio-professional category, respectively.

The number of children hospitalised at least once was not different between cases and controls in the SPC⁺ group ($p = 0.3270$), but was significantly higher in cases than in controls in the SPC⁻ group ($p = 0.0063$) (figure 4A).

The number of children having been anaesthetised at least once was not different in cases and controls in the SPC⁺ group ($p = 0.8690$), nor was it in the SPC⁻ group ($p = 0.147$) (figure 4B).

3.5. Effect of hospitalisation and anaesthesia

In the whole sample ($n = 144$ pairs), Chi² analysis of case-control pair distribution in the three subgroups (i) non-hospitalised, ii) hospitalised but not anaesthetised and iii) hospitalised and anaesthetised, at least once) revealed significantly different distributions among groups (Chi², 9.67, df 2, $p = 0.0257$). In the SPC⁻ group, subsequent two group comparisons using two-tailed Fisher's exact test revealed significant difference in i) non-hospitalised *versus* hospitalised but non-anaesthetised cases ($p = 0.049$) and ii) in non-hospitalised *versus* hospitalised and anaesthetised cases ($p = 0.0065$) (figure 5).

4. Discussion

In a population of 414 children with LD i.e. dyslexia and related conditions, we found i) that 107/414 had a medical history which could explain, at least in part, their difficulties (see figure 1) and ii) that these children with LD were hospitalised more frequently than their normally reading siblings prior to the age of five years, a temporal window at the end of which oral language is normally fully established. Cases were also more frequently anaesthetised than controls, although the magnitude of the effect was lower. These results suggest that hospitalisation *per se* could be more deleterious than surgery and anaesthesia in terms of cognitive disorders or that it could be a surrogate of the toxic effect of an ongoing disease on brain development.

These results were significant only in children from families of low socioeconomic status (SES), a variable that is known to be associated with some specificities of neurodevelopment in some brain regions [21].

Finally, the distribution of anaesthesia between cases and controls, showing significant difference when taking all procedures into account but not when considering only simple procedures (figures 3.B. and 3.C.), suggests that some specific types of surgeries, as complex surgeries, although performed in small numbers of children, contributed to the significance of our results. This suggests that surgery complexity by itself represents another confounding factor that could have played a role in previous studies.

Recent large prospective studies [15,16] have shown that a single anaesthesia exposure does not elicit detectable long-lasting brain disorder, which does not rule out possible infraclinical effects on brain development. Indeed, it is now well known that the brain is able to compensate sometimes very severe injuries like stroke or brain trauma through recruitment

and hyperactivity of spared regions [23-25] or reorganisation of functional regions at neuronal network [24] and anatomical levels (e.g. changes in interhemispheric lateralisation) [26], even late in life. These changes may underlie the stability of a normal phenotype following some brain injuries. In addition, compensating behavioural strategies can be elicited after various kinds of brain lesions [27]. Possibly, such compensating mechanisms and strategies could underlie these recent negative clinical results after exposure to a single anaesthesia, in apparent contradiction with preclinical and retrospective data. Recent results suggest that such compensating mechanisms could be overwhelmed in case of multiple procedures [17].

On the other hand, the quite high frequency of brain injuries of various kinds or of conditions placing the neurological prognosis at risk in the history of children with LD in our study population (see figure 1) suggests the existence of biases that could have played a role in the results of previous studies in the field of the neurotoxicity of general anaesthetics [19].

Also, it is known that an altered environment may have long-lasting effects on individual brain development [28]. One can speculate that this is the case when a child is hospitalised early in life. This is in accordance with the fact that hospitalisations and associated diseases, with or without anaesthesia exposures, could be the main determinant of disruption of the setting up of learning abilities, rather than anaesthesia itself. Hence, previous retrospective studies showing a correlation between the number of anaesthesia exposures and LD may have neglected the fact that the disease, on the one hand, and simultaneous hospitalisation, on the other hand, may have a deleterious effect by themselves, especially when repeated, constituting a level of stress sufficient to disrupt normal development.

Cohorts of children with LD have provided the first line of evidence supporting a long-lasting effect of procedures under general anaesthesia [5-10]. This group of conditions is underpinned by an important genetic contribution but epigenetic factors may influence their occurrence as well, i.e. stress may generate adaptive responses resulting in a shortening of the maturation of attention networks [29]. Using a case-control design comparing two siblings, we aimed to control for as many environmental factors as possible, excluding factors related to diseases and their treatments. More precisely, comparing a normally reading sibling to a dyslexic sibling is one way to compare different conditions (no hospitalisation *versus* hospitalisation with or without anaesthesia) within a similar genetic and environmental background. Indeed, our observation in upper *versus* lower SPC is in line with this important role of the environment. This could indicate that the possible deleterious effect of hospitalisation in terms of LD appears only in SPC families, possibly due at least in part to the difficulty of accessing education.

Thus, hospitalisation in all its components could represent a situation at risk of alterations of ongoing brain development more than anaesthesia *per se*, a hypothesis that warrants further research for confirmation. Indeed, the illness and/or altered environment induced by hospitalisation could promote disruption of the normal setting up of learning abilities rather than anaesthesia itself. On the other hand, exposure to anaesthetics could have been part of global modifications of the environment related to hospitalisation or could have interplayed with illness-related changes, rather than simply being a direct cause of learning disabilities in previous studies.

Our study has some limitations. First, it is a retrospective approach. Second, we lack information about the exact anaesthesia protocols to which children were exposed, although anaesthesia was not overrepresented in cases compared to controls. Also, we were

only able to collect data on the number of hospitalisations, but not on the exact length of hospital stay and the complexity of surgeries was determined empirically (see chapter 3.3. and Table 3, supplemental data). Finally, the results observed were significant only in a subgroup of patients (the SPC - group), resulting in a relatively low power. Despite this low power, the significance of the results testifies to the rejection of the null hypothesis.

Yet, now that we know, in a retrospective case-control design, that children with LD *versus* children without LD are more frequently seriously ill, in the whole population but more especially in SPC families, it would be interesting to determine prospectively if children hospitalised more than once before five years of age do face greater difficulties at school. In this case, one should consider providing educational guidance in weeks or months following hospitalisation in at-risk populations, especially in families with medical history and low income.

6. Conclusion

In conclusion, in this cohort of 144 cases compared to controls, we found that children with learning disorders were ill and hospitalised significantly more frequently than their siblings without learning disorders before the age of five years. This difference was seen in families of low socio-professional categories. These children were more frequently anaesthetised as well, although this difference did not reach statistical significance.

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Tables and figures legends

Table 1: Reasons for hospitalisation (excluding anaesthesia exposures) before the age of five years; N = number of children per category, cases/controls. Diagnoses are counted as having occurred at least once in one child (i.e. several episodes of bronchiolitis in one child gives rise to a single diagnosis of bronchiolitis in the same child). Misc. (haematoma, ethmoiditis, oesophagitis, burn, cardiac murmur, neonatal varicella, thrombocytopenia, benign parasitosis, toxic ingestion, neonatal tachycardia, allergy, epiphysiolysis)

Table 2. Types of surgeries performed before the age of five years. N = Number of patients per category, cases/controls. Procedures are counted as having been performed at least once in one child (e.g. several procedures for adenoidectomy in one child gives rise to a single count of adenoidectomy in the same child).

Figure 1. Reasons for exclusion. Conditions or circumstances invalidating the comparison between cases and controls are shown. (N): number of cases with the condition.

Figure 2. Mean number of hospitalisations (two left bars) and of anaesthesia procedures (two right bars) per child, in cases and controls, respectively, before the age of five years. ** $p < 0.01$ in two-tailed paired t-test.

Figure 3. Total numbers of hospitalised cases and controls (panel A), anaesthetised cases and controls (panel B) and anaesthetised-for-simple-surgery cases and controls (panel C). * $p < 0.05$ ** $p < 0.01$ in Fisher exact test.

Figure 4. Total numbers of hospitalisations (panel A), and of anaesthesia exposures (panel B) in cases and controls, in high (upper panels, SPC⁺) and low (lower panels, SPC⁻) socio-professional categories.

Figure 5. Distribution of the three case-control groups corresponding to the three combinations (i) non-hospitalised, ii) hospitalised but not anaesthetised and iii) hospitalised and anaesthetised, in all socio-professional categories (SPC, left panel), upper socio-professional categories (SPC⁺, middle panel) and lower socio-professional categories (SPC⁻, right panel).

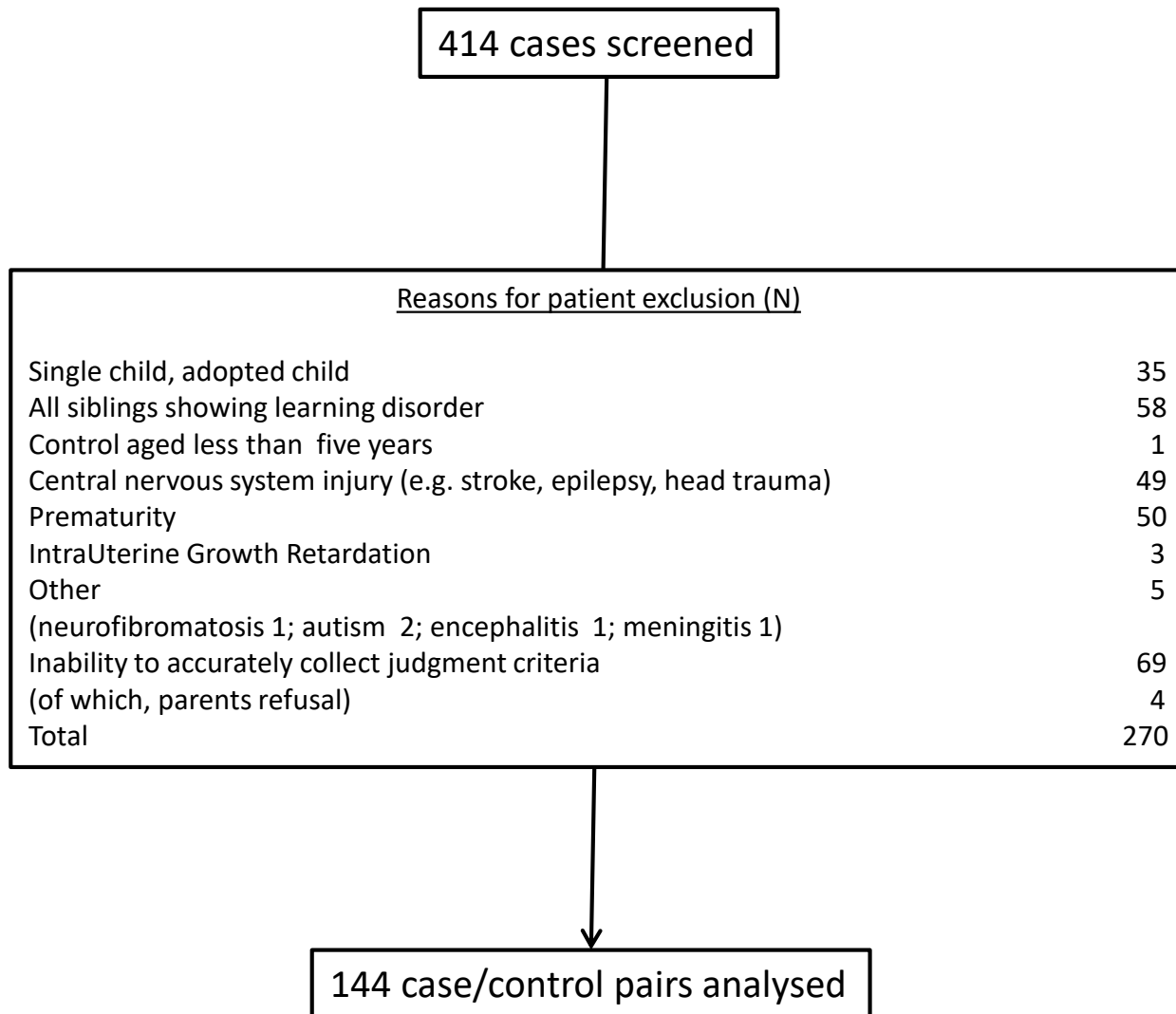


Figure 1. Reasons for exclusion.

Figure 2

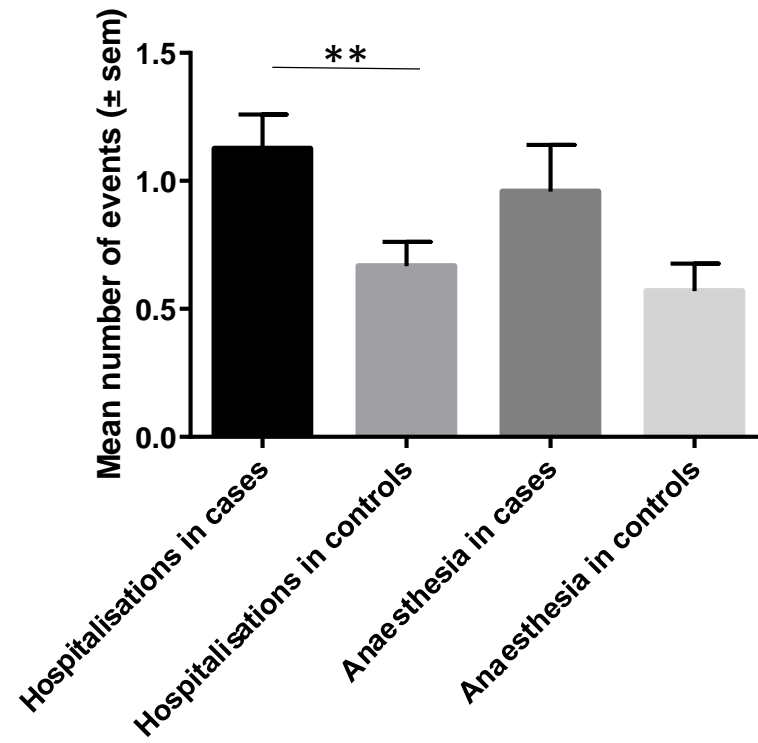


Figure 3

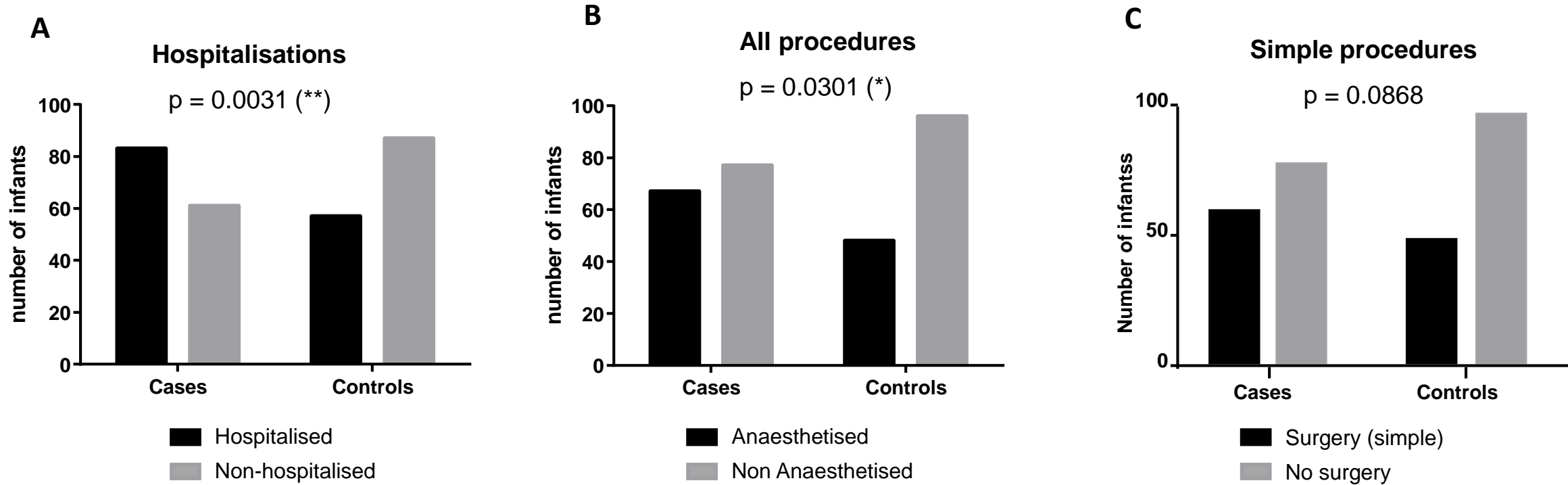


Figure 4

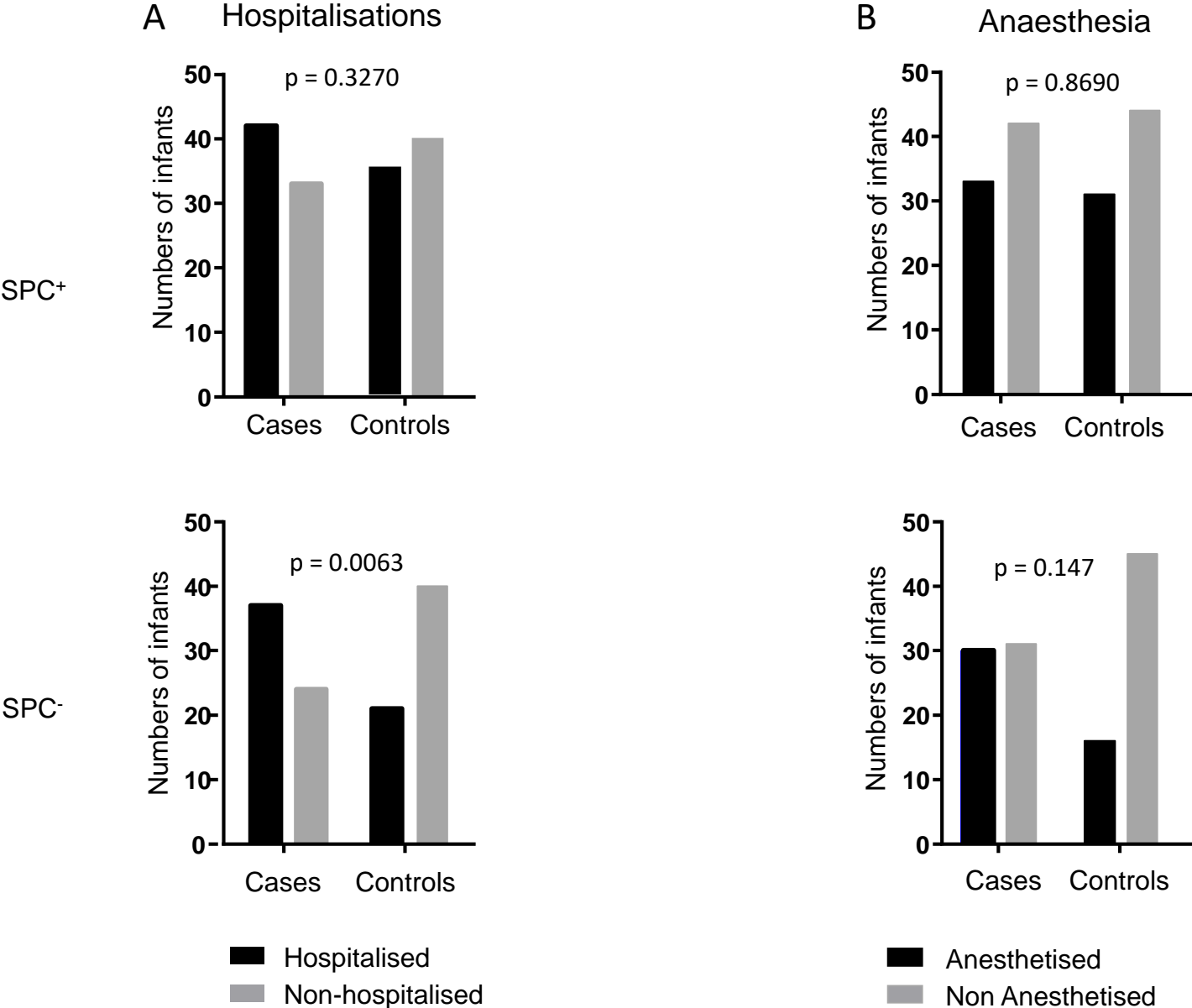
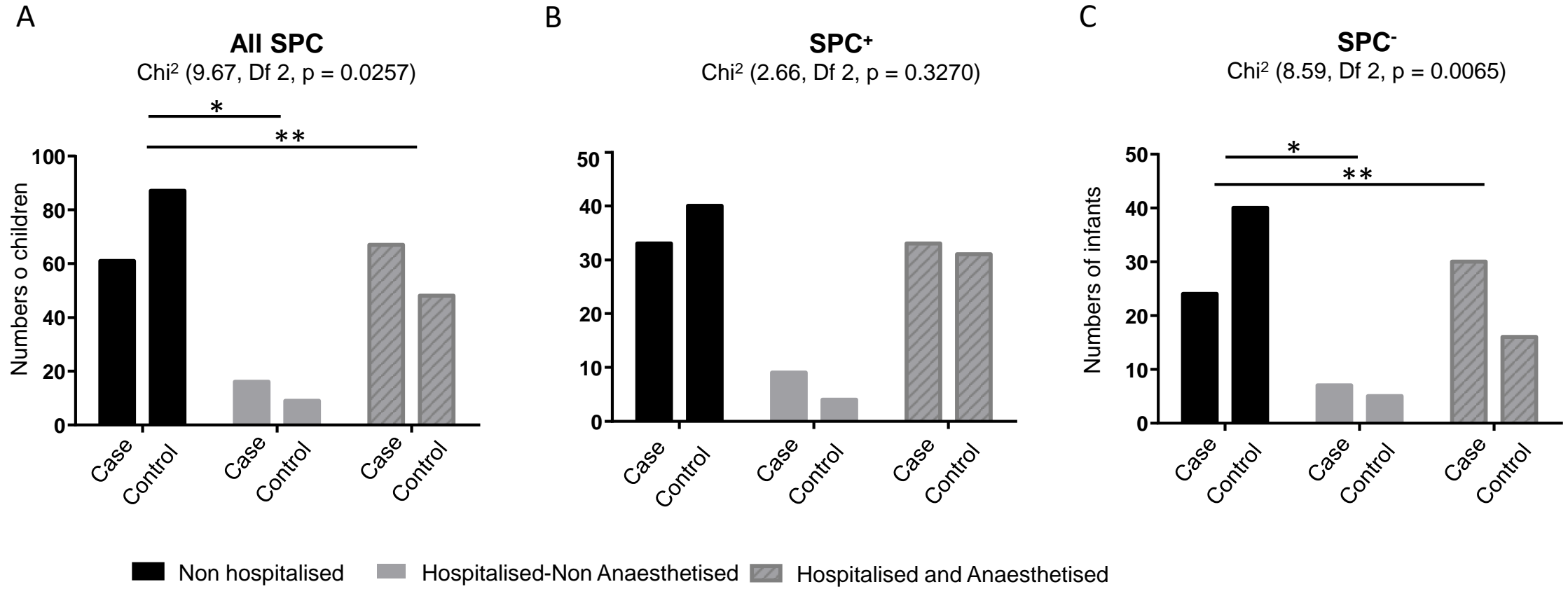


Figure 5



	Cases (N)	Controls (N)
Bronchiolitis, asthma	18	7
Pneumonia, flu	2	2
Fever	6	1
Gastroenteritis	6	3
Urinary infection	3	2
Miscellaneous	13	5

Table 1. Reasons for hospitalisation (excluding anaesthesia procedures) before the age of five years; N = number of children per category, cases/controls. Diagnoses are counted as having occurred at least once in one child (i.e. several episodes of bronchiolitis in one child gives rise to a single diagnosis of bronchiolitis in the same child). Misc. (haematoma, ethmoiditis, oesophagitis, burn, cardiac murmur, neonatal varicella, thrombocytopenia, benign parasitosis, toxic ingestion, neonatal tachycardia, allergy, epiphysiolysis)

	Cases (N)	Controls (N)
Ear-Nose-Throat	41	26
Thoracic	2	1
Abdominal	6	6
Orthopaedic	4	4
Urologic	12	8
Peripheral (sutures, skin lesions, etc.)	6	5
Fracture, painful pronation	3	2
Endoscopy, radiology	5	0

Table 2. Types of procedures performed under anesthesia before the age of five years. N = Number of patients per category, cases/controls. Procedures are counted as having been performed at least once in one child (e.g. several procedures for adenoidectomy in one child gives rise to a single count of adenoidectomy in the same child).