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ADVANCES ON INFANTILE COLIC

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ABSTRACT BOOK

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Parental education for the management of colic: how the evidence can inform paediatricians?

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The causes of infantile colic remain suprisingly difficult to understand. It has been postulated that the parent/infant interaction may be a contributing or causitive element in infantile colic. As such, educational and training interventions for parents and try to modify this interaction have been used. These interventions will be explored, their effectiveness discussed in the context of the existing evidence and a wider discussion of reporting of educational interventions within healthcare will be undertaken.

Relationships, and Distinctions, In-Between Infant Crying and Sleeping Problems: Recent Evidence and Implications for Research and Practice

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Infants who cry a lot, or who are unsettled at night, are common sources of concern for parents and costly problems for health services. For example, they have been estimated to cost the U.K. National Health Service over £65 million per year. More rarely, but tragically, infant crying can elicit shaking and other forms of parental abuse, leading sometimes to infant brain damage or death. These findings emphasize the need to understand the origins of infant crying and sleep-waking behaviours and to distinguish the features which lead to poor outcomes.

Some researchers studying these issues have argued that infant prolonged crying and poor sleeping have a shared origin in disorders of 'infant self-regulation'. Others argue that the two types of problematic behaviour have distinct causes. In particular, the unexplained bouts of crying that occur in around 20% of young infants have been attributed to gastrointestinal disturbance and pain, leading to the clinical designation of 'infant colic'. Infant sleep problems are viewed as the results of impairments in the circadian and homeostatic systems controlling sleep and waking. These explanations share the assumption that the behaviours involved are due to disturbances of infant health.

In contrast, I will present evidence for a developmental approach to infant crying and sleeping problems. This considers them both to be the outcomes of normal developmental processes guided by the external, care-giving environment. However, it regards them as distinct phenomena, with different causal pathways and histories, so that infants who cry a lot are not especially likely to have sleeping problems. Prolonged infant crying is attributed to normal maturational changes in the infant central nervous system, while unsettled infant night-time behaviour is due to delay in developing the ability to

resettle back to sleep without crying out after waking in the night. Parenting factors are important both in defining what is problematic and in providing an environment that supports infant development. However, the parenting factors that influence prolonged crying and settled infant behaviour at night are quite different.

Unlike explanations of infant crying and sleeping problems that attempt to treat organic disturbances within infants, the implication of this developmental explanation is that health services need to focus: (1) on supporting parents in how to contain crying in 1-3 month-old infants; (2) on explaining how infants develop settled behaviour at night; (3) on identifying social vulnerability; (4) on preventing adverse long-term outcomes. The last part of this presentation will propose ways in which health systems can be developed to meet these family needs.

Heart rate response to crying: the influence of hormones in expectant fathers

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For a very young infant the primary way of communicating with the outer world is mainly through crying. The crying provides the parents with information about the infants' well being. This will trigger the parent to react accordingly, i.e. to attend the infant. Various studies have shown that infant crying causes a physiological response in all adults, e.g. heart rate (HR) acceleration. Even though there are noticeable differences in the way that individuals respond towards an infant in distress, behaviourally as well as physiologically. These individual differences may originate from differences in the levels of hormones that have been connected in the past to parental bonding. Hormones that have been opted to influence individual differences in caregiving behaviour are oxytocin and vasopressin.
To date, research concerning caregiving behaviour and interest has focused mainly on the mother; the role of the father on the other hand has been rather neglected. However, in our modern society the view of fatherhood is shifting from solely being a financial provider towards a parent that engages more and more in the caregiving tasks. This increase of fathers actively participating in the upbringing of their offspring raises the need for research concerning fatherhood.
In this study, we examined whether fathers-to-be react differently to the sound of a crying baby as compared to childless cohabiting male controls. In addition, we investigated the possible influence of hormones on cardiac responses (HR, vagal tone) while listening to the crying tapes. To this end basal levels of oxytocin and vasopressin were assessed, and during the laboratory visit, these hormones were also administered by means of nasal sprays.

Inconsolable Infant Crying and Maternal Post-Partum Depressive Symptoms

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Infant colic, traditionally defined as paroxysms of fussing and crying, lasting greater than three hours per day for greater than three days per week peaks at about 6 weeks of age and occurs in about 20% of infants. For research, colic is best described using a validated crying diary. Colic is known to be stressful for care givers and or associated with maternal depressive symptoms, premature weaning, frequent formula changes, and shaking baby syndrome. Our clinical experience in addition to limited research findings suggests a special and important contributor to stress and/or maternal depression of inconsolable crying over and above the standard definition of colic. Inconsolable crying engenders feelings of frustration and lack of self-efficacy. We therefore conducted a retrospective cohort analysis of data from the control arm of a completed randomized control trial to investigate the longitudinal association of inconsolable infant crying at 5-6 weeks of age with maternal depressive symptoms at 8 weeks post-partum among 587 recruited mothers. Results show that of the 60 mothers who met the Edinburgh Postnatal Depression Scale (EPDS), for "possible depression" scored ≥ nine, at 8 weeks post-partum had an odd ratio of 4 if mothers reported greater than 20 minutes of inconsolable crying per day and an OR of 2 for mothers whose infants fit the definition of colic. These associations persisted after adjusting for baseline depression symptoms. The findings of this study have important clinical and research implications. First, asking a mother about her ability to sooth her infant may be more relevant for potential intervention than questions about crying and fussing duration alone. Second, the impact of inconsolable crying should also be measured in other studies having to do with causes or prevention of infant crying.

Pyrosequencing analysis of the faecal microbiota of colicky infants treated with probiotics

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Abstract
Lactobacillus reuteri DSM 17938 has earlier been shown to improve the symptoms of infantile colic. Although infants with colic have differences in the microbial populations compared with control infants, the role of the intestinal microbiota in infantile colic is not fully understood. We have addressed this by studying the global microbial composition, using large-scale DNA sequencing of 16S rRNA genes, in faecal samples from colicky infants given *L. reuteri* DSM 17938 or placebo. Twenty-nine exclusively breastfed infants, 10-60 days of age were enrolled and randomly assigned to receive an oil formulation containing either *L. reuteri* DSM 17938 (10^8 colony-forming units) or a comparable placebo once daily for 21 days. Analysis of the gut microbiota was performed using 454-pyrosequencing analysis of DNA prepared from faecal samples (day 0 and 21). The structure of the obtained data was explored by using permutational multivariate analysis of variance and effects of different variables were visualized with ordination analysis. The infants' faecal microbiota were composed of *Proteobacteria*, *Firmicutes*, *Actinobacteria* and *Bacteroidetes* as the four main phyla, but the composition of the microbiota had very high inter-individual variability with Firmicutes/Bacteroidetes ratios varying from 4000 to 0.025. On an individual basis, the microbiota was, however, relatively stable over time. Treatment with *L. reuteri* DSM 17938 did not change the global composition of the microbiota, but when comparing responders with non-responders the group responders had an increased relative abundance of the phyla *Bacteroidetes* and genus *Bacteroides* at day 21 compared with day 0. Furthermore, the phyla composition of the infants at day 21 could be divided into three enterotype groups, dominated by *Firmicutes*, *Bacteroidetes*, and *Actinobacteria*, respectively. In summary, *L. reuteri* DSM 17938 did not affect the

global composition of the microbiota. However, the increase of Bacteroidetes in the responder infants indicated that a decrease in colicky symptoms was linked to changes of the microbiota.

Intestinal microbiota of infants with colic: development and specific signatures

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Up to around a quarter of all infants spend a great part of their first months of life crying excessively and not responding to parental soothing attempts. This phenomenon has been termed 'infant colic' and is often a source of great worry for parents, even though it mostly resolves by 3 or 4 months of age. There is accumulating evidence that the intestinal microbiota in infants with colic differs from that of healthy controls. In studies that were mostly based on traditional culturing approaches, the stools of colicky infants were found to display reduced diversity in microbiota, lower counts of Lactobacilli and higher numbers of gram-negative bacteria. Additionally, recent randomized control trials giving probiotics to colicky infants report decreases in crying by 2-fold or more, significantly more often in the group of infants receiving probiotics than in those receiving placebo. However, these studies pertain infants already diagnosed with colic and usually of over 6 weeks of age. In a recent study, and by means of comprehensive and deep analyses of more than 1000 intestinal phylotypes, we found that infants with colic showed lower microbiota diversity and stability than control infants in the first weeks of life. Already as early as at 2 weeks after birth, specific differences in the abundance of certain bacteria were found when fecal samples of colic and control babies were compared. Although the study was aimed to unravel associations, it is tempting to assume that the observed microbial signatures may be, at least partially, causative of many colicky infants' excessive crying.

Our other genome

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Our "other" genome is the collective genetic information encoded in all the microorganisms which are living on and within us. Collectively known as the microbiome, these microbial cells outnumber human cells in the body by more than ten to one, and the genes encoded by these organisms outnumber the genes in the human genome by over 100 to one.
How these organisms contribute to and affect human health is still poorly understood but the emerging field of metagenomics promises a more comprehensive and complete understanding of the human microbiome.
By combining next-generation sequencing with high-density microarrays in the European project on the metagenomics of the human intestinal tract (MetaHIT, http://www.metahit.eu) we generated metagenomics and metatranscriptomics data for over 400 individuals.
This combined data reveals clusters of co-existing species showing differences in pathway and gene function activity, suggesting a division of labor between the bacterial species inside the human gut microbiome and their potential role in various diseases like obesity, IBD, CD and infantile colicky.

Impact of diet on gut microbiota in children living in different environments

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Unraveling the ecology and evolutionary history of human gut microbiomes has recently become possible through the advent of metagenomics. Large-scale projects such as the European Metagenomics of the Human Intestinal Tract[1] and the US Human Microbiome Project[2] have made substantial progress towards this goal. Both host and environmental factors can affect gut microbial ecology over a lifetime[3,4] . Dietary habits are considered one of the main factors contributing to the diversity of human gut microbiota[5]. Studies on traditional populations living in isolation from the globalized world are especially valuable since variables that correlate with microbiota diversity, such as diet, history of antibiotic use, and environmental exposures can be precisely measured. Historically, the microbial ecosystem of the digestive tract was specific for a geographic area, as much as the flora and fauna of an ecosystem are geographically distinct. A clear example of this richness and diversity is that currently in Africa, the microbial composition is very different from that described in Europe or America.
In a recent paper we showed how levels of *Prevotella* were enriched in children from a rural African village with a high-fiber diet[6], similarly to children and adults from Malawi and Venezuela whose diet was dominated by plant-derived polysaccharide foods such as maize and cassava[7]. Interestingly the ratio of *Prevotella* and *Bacteroides* has been more recently shown to correlate well with the overall pattern of diversity across healthy adults[8,9] possibly reflecting differences in diet. *Bacteroides* was associated with a long-term diet rich in animal protein, several amino acids and saturated fats, and *Prevotella* was associated with carbohydrates and simple sugars[9].

These results indicate that the globalization of the microbial population of our digestive tracts is likely the result of the industrialization and standardization of food chain products that homogenizes the microorganisms, which we ingest. Western developed countries successfully controlled infectious diseases during the second half of the last century, by improving sanitation and using antibiotics and vaccines. At the same time, a rise in new diseases such as allergic, metabolic disease and autoimmune disorders like inflammatory bowel disease (IBD) both in adults and in children has been observed[10]. It is hypothesized that improvements in hygiene together with decreased microbial exposure in childhood could be responsible for this increase[11,12]. We showed that dietary fibers are another critical element in this equation. When comparing children from rural Africa with children from an European country with different diets what is surprising is that the decrease in fibre intake and loss of key fibre degrading microbial species seems to have reduced the amount of gut healing molecules, such as short chain fatty acids (SCFASs), naturally present in ancestral fibre rich diets[6].

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Probiotic Therapy and Microbiological Programming in the Colic Infant - a Randomized, Controlled Trial

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Objective: To evaluate the effect of *Lactobacillus rhamnosus* GG on infant colic crying and microbiological programming of breast- and formula-fed infants.

Patients and Methods: Infants with colic (n=30) were enrolled during the first 6 weeks of life. All families received behavioral support, breast-feeding mothers were given lactation support and formula-fed infants extensively hydrolyzed casein formula. The randomized, double-blind intervention embloyed of *Lactobacillus rhamnosus* GG ($3.4x10^9$ cfu/day) or placebo for a 4-week study period. Fecal calprotectin and gut microbiota composition by qPCR were evaluated before and after the intervention. The gut microbiota of colic infants was compared with that of healthy infants.

Results: In 30 infants with colic, crying times ranged between 180 to 720 minutes per day. During the study period, the daily crying time decreased 68% in the probiotic group and 49% in placebo (p=0.0495). The daily crying time was 70 minutes *vs*. 138 minutes, respectively, at the end of the study (p=0.03). During the study period, the numbers of *B. lactis* increased in 47 % of infants receiving probiotic compared to 13 % of those receiving placebo (p=0.02). The number of *Bifidobacteria genus* was lower in the feces of colic infants compared to healthy infants.

Conclusion: Our results suggest that probiotic intervention alleviates symptoms of infant colic. However, further studies are needed to reveal the mechanisms of probiotic intervention on colic.

Infantile colic and food allergy

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Food allergy (FA) is an adverse immune response toward food proteins. Food allergy often presents to clinicians with a symptom complex which develops after ingestion of foods, with time of onset ranging from minutes to days. Its well known that FA is associated with gut microbiota dysbiosis and dismotilty of gastrointestinal (GI) tract. Although, the etiology of infantile colic (IC) remains controversial, both conditions, dysbiosis and dysmotility, have been advocated as crucial pathogenetic factors. There is some evidence that IC is associated with cow's milk allergy (CMA), but the strength of this relationship is not well-defined. Infants who are experiencing symptoms of CMA have a high rate (44%) of colic, and extensively hydrolyzed formulas are more efficacious for colic than antacids or low-lactose formula. However, the role of FA as opposed to other causes among those with colic and without other symptoms of FA remains controversial. For example, there does not seem to be an increased rate of atopy in infants with colic. In regard to trials of therapy, a meta-analysis of 27 trials identified through Medline and the Cochrane Controlled Trials Register concluded that IC should preferably be treated by reduced stimulation (effect size 0.48) and a 1-week trial of substitution of cow's milk formula with hypoallergenic formula (effect size 0.22 based on 2 studies). The formula suggested by these Authors for substitution was extensively hydrolysate, because soy formula is not recommended for the treatment of FA in infants aged less than 6 months. On the other hand, no positive impact in improving symptoms of IC has been observed with partially hydrolyzed formulas since they are not hypoallergenic. In a previous randomized controlled trial in which mothers eliminated diary foods, eggs, peanuts, tree nuts, wheat, soy, and fish from their diet, the

primary endpoint, reduction in “cry/fuss” duration of > 25% from baseline, was significantly better with more responders in the low allergen diet group compared with the control group and with an absolute risk reduction of 37%. However, in breastfeeding mothers, there is limited evidence that a fully hypoallergenic exclusion diet may be helpful in improving IC symptoms. In conclusion, the role of FA among infant with IC without other symptoms of atopy remains controversial and in need of additional study. However, where there is a suspicion of FA (i.e., atopy risk, other signs or symptoms of FA) a short trial with an extensively hydrolysed formula or, if breast fed, with maternal elimination diet may be considered a reasonable option. Later, a oral food challenge should confirm a true diagnosis of FA.

Calprotectin as a marker of bowel inflammation

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Abstract
In recent years the need for a non-invasive diagnostic tool that would help to discriminate between organic (e.g.: infections, food allergy-related disorders, inflammatory bowel diseases) and functional gastrointestinal disorders (e.g.: Toddler diarrhea, irritable bowel syndrome, infant colic) directed research towards potential immunological markers. A great number of non-invasive bio-markers have been proposed, including eosinophilic cationic protein, elastase, esterase, myeloperoxidase, lysozyme, lactoferrin, and calprotectin (1-3). Compared to other biomarkers, calprotectin (also called MRP8/14, calgranulin A/B , cystic fibrosis antigen or S100 A8/A9) may offer advantages based on its biological characteristics. Calprotectin is a 36.5-kDa, calcium and zinc binding polypeptide which constitutes about 60% of soluble cytosol proteins in human neutrophils (4). It is also found in monocytes, keratinocytes, muscle tissue and infiltrating tissue macrophages (4). When bound to calcium it becomes resistant to proteolysis and colonic bacterial degradation. This make it stable for up to 1 week at room temperature and facilitate its determination in feces (3,5). Calprotectin is involved in the regulation of the inflammatory process, participate to the early innate immune response and exert antimicrobial, anti-proliferative and apoptotic properties (4-6). Fecal calprotectin is a direct measure of mucosal inflammation activity and becomes detectable when intestinal inflammation is still at an insufficient level to cause an increase in serum inflammation markers (2).
In the last decade fecal calprotectin has been proposed as a marker to rule out acute and chronic intestinal inflammatory diseases in children with typical gastrointestinal symptoms. Many studies demonstrated its diagnostic utility in identifying children and adults with inflammatory bowel disease (7,8) and correlate with the degree of disease activity (9,10).

The detection of elevated levels of fecal calprotectin in healthy infants during the first few weeks of age, limits their use as screening test for intestinal inflammatory diseases in early life [11]. Despite this evidence, the measurement of calprotectin in the serum has been proposed to identify neonates with necrotizing enterocolitis (12). Recent studies have shown higher fecal calprotectin levels in infants with irritable bowel syndrome (IBS) and colics, compared with healthy controls (13,14). Additionally a correlation was found between fecal calprotectin concentration and IBS clinical presentation severity (14). However, these studies do not provide data on diagnostic accuracy in distinguish between organic and functional gastrointestinal disorders. Despite significant limitations, these evidences suggest the presence of a subtle inflammatory process underlying functional gastrointestinal disorders and open new perspectives on their pathogenesis. Fecal calprotectin may play a role that could be revealed in further, specifically designed, studies. Changes in microflora, permeability, calprotectin excretion and other inflammatory biomarkers, should be investigated to clarify if a continuum exists between inflammatory conditions and intestinal functional diseases.

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Abdominal pain in infants and children

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Functional abdominal pain (FAP) and irritable bowel syndrome (IBS), both of which typically present with chronic abdominal pain, are common complaints in the pediatric population. Estimates on the prevalence of abdominal pain are varied, but community- and school-based studies have reported that as many as 13–38% of children and adolescents experience abdominal pain weekly, with up to 24% of children reporting symptoms persisting longer than 8 weeks. For the vast majority of patients, an underlying inflammatory, anatomic, metabolic or neoplastic cause for recurrent abdominal discomfort is not found on evaluation. A significant proportion of these patients are subsequently diagnosed with FAP or IBS. Both entities are included under the larger heading of functional gastrointestinal disorders (FGIDs), which are characterized by chronic or recurrent gastrointestinal symptoms that are not explained by structural or biochemical abnormalities. The diagnosis of FAP or IBS is symptom-based and new criteria have been defined by the Rome III group. In addition to recurrent abdominal pain, children with IBS also experience disturbances in defecation, ranging from lumpy or hard stools to loose, watery stools or both. Functional abdominal pain and IBS have been associated with significant impairment in children and adolescents. Children with FAP have self-reported quality of life scores lower than healthy children and comparable to children with inflammatory bowel disease. Increased rates of school absenteeism, health-care utilization and family disruption are also common. The financial burden of FAP and IBS in children is not exactly known but is probably significant, considering the frequent need for multiple medical visits and extrapolating data, which estimate that billions of dollars are spent each year for the management of adults with IBS.

The Capability of Skin Conductance to Monitor Pain Compared to other Physiological Pain Assessment Tools in Children and Neonates

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Background: In some European countries and the US it is mandatory to assess and treat pain. In Pubmed there are more than 240 papers when searching for "skin conductance" and "pain".
Aims: The aim is to review the utility of the skin conductance responses (SCR)/sec to assess pain in infants and children.
Study design: Two searches in Pubmed, where one includes the key words "skin conductance", "pain", and "children". Search two included "skin conductance", "pain", and "infants". The finds in these searches are discussed and compared with other physiological pain assessment tools.

Outcome measures: Search one, regarding children, included twelve papers, and search two, regarding infants, included 20 papers.

Results: All the found papers show that the SCR/sec increases during defined painful procedures. Postoperatively, at intensive care units, and at neonatal units, the SCR/sec shows high sensitivity to monitor pain, but a lower specificity. The the SCR/sec is the most accurate means to assess pain when compared to the HR and peripheral oxygen saturation.

HR is influenced from respiratory rhythm, changes in blood volume status, drugs acting on the blood circulation, environmental temperature, and emotional stress, and is therefore less specific to pain than the SCR/sec which only is influenced from emotional stress. For infants and children, variation for SCR/sec is low compared to HR and peripheral oxygen saturation when the patients are at the same pain/discomfort level.

Conclusions: The SCR/sec could be adjunctive warning tool for when to validate possible pain.

Actigraphy and Infantile Colic

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1. Introduction

In last century, especially in the last decades, Medicine has experienced the major progress ever known in that discipline, however protocols for diagnosis and therapy in a number of high-prevalence pathologies are still susceptible of improvement. The lack of full knowledge on these pathologies may explain this issue; that is the case of the infantile colic (IC). This pathology, whose prevalence yields the 16% of children under 3 months, significantly affects the quality of life of the affected children and their families, which has generated great interest of in the community. Despite the aetiology is not fully understood and the therapy is not well defined, several scientific contributions have arisen on both concerns: for instance, the idea of a "multifactorial pathology" is widely accepted on the aetiology and the removal of the cow milk protein from the patient's diet has shown promising results as a therapy. These findings, however, cannot be used in the daily patient-care since they have not been settled for several reasons such as the trial size limitations. This being the case, daily clinical practice is modulated by research, but research is limited (even blocked) by some clinical-related aspects such the economic and human cost of the clinical trials. This case is not unique; the management of the ADHD (attention-deficit hyperactivity disorder), for instance, suffers from similar difficulties. For these cases in which the underlying pathology affects the patient activity/motility, the joint use of actigraphy and Signal Processing techniques seems appropriate to overcome that predicament as an inexpensive manner of monitoring high numbers of patients without the need of directly involving a great deal of medical staff. In other words, the application of signal processing techniques over actigraphy registries may be useful in three ways: 1) the actigraphic analysis provides valuable information to increase the understanding of the IC; 2) the automatic analysis of actigraphy registries reduce the economic and human impact of the

clinical trials, which makes large-scale clinical tests affordable; and 3) consequence of 1) and 2), actigraphy and signal processing may contribute to speed up the process by which the advances from research are included in the clinical protocols for the IC management ("from the laboratory bench to the patient bedside"). This lecture is aimed at showing the potential utility of actigraphy and Signal Processing for the assessment of IC in the three ways described above. To this end, a description of the most relevant findings on IC is given together with some concluding remarks on these findings.

2. Actigraphic Assessment of the Infantile Colic

Actigraphy can be defined as the technique that allows the practitioner to non-invasively measure the proper acceleration of an object or a part of the body. Clinical applications of actigraphy are devoted to the quantitative assessment of three aspects, namely: night-sleep quality, chronobiological rhythms of activity and raw activity. This section shows the most relevant results of the usage of actigraphy and Signal Processing techniques for the assessment of the IC in each aspect of those of above.

2.1. Sleep Quality Assessment

Actigraphic sleep reports have become an inexpensive substitute for polysomnography (PSG) to quantitatively assess the quality of sleep. Thanks to the well-known *sleep scoring algorithms*, such as the one of Sadeh, the parameters characterizing the sleep obtained from actigraphy registries are close to those obtained by PSG (correlation coefficient = 0.9). Unfortunately, this modality of analysis has not shed light on the IC management (at least, as might be initially expected), since the discriminant analysis between cases (IC-affected children) and controls (healthy children) did not bring any statistically significant difference ($p>0.3$ for all the parameters forming the sleep pattern). This result shows that IC does not affect the quality of sleep, at least in a significant way.

2.2. Chronobiological Rhythm of Activity

Biological rhythms are inherent to human nature; thus, the alteration of these rhythms is either the cause or the consequence of several

disorders (melatonin production and insomnia, for instance). As for the activity rhythms, it has been demonstrated the existence of a circadian rhythm (twenty four hours period) in which the daylight determines both the peak and the valley of activity. Our experiments in this line show: 1) the existence of circadian rhythm in both the control and the case groups; and 2) the average activity (MESOR parameter) is higher for the case group ($p<0.05$). Whereas the second result is to be expected according to the symptoms of the IC, the first result is quite noticeable due to the high amount of sleep-awake episodes that usually children under one year experience, especially those affected of IC.

2.3. Raw Activity Analysis

From the Signal Processing point of view, this modality of analysis is the most powerful since a broad range of methods may be used for analysis. However, contrary to what one might think, there is a great variety of potentially useful methods that have not been applied so far. According to the literature, methods derived from the classical statistical analysis are the most commonly used to assess the IC through actigraphy. Among the set of parameters resulting from this modality, the *percentage of sleep* shows the highest capability to discriminate between cases and controls; specifically, that parameter indicates that cases sleep longer than controls ($p<0.002$). Regarding other non-widespread methods, those aimed at assessing the variability/regularity of any registry by means of non-linear magnitudes deserve special attention. Among them, bearing in mind the statistical properties of the actigraphy registries, Symbolic Dynamics is a suitable method to analyse this sort of signals, since it operates with a simplified version of the signal instead of the original. The output of this analysis is a set of probabilities that represent the behaviour of the registry in terms of variability. A discriminant analysis based on this method shows large differences between cases and controls ($p<0.00002$), which allows for the construction of classifiers (automatic diagnosis system) with accuracy up to 0.96. Successful outcomes of this method are, however, hard to interpret due to the complexity of the analysis carried out.

3. Conclusions

The joint use of actigraphy and Signal Processing techniques is a valuable tool to deal with the management of the IC from both the research and the clinical point of view. Accordingly, the actigraphic assessment of IC has revealed that: 1) the circadian rhythm of activity is not altered by IC, 2) IC-affected children sleep longer than healthy children but with lower quality, and 3) the activity of IC-affected children is more intense (even though their longer sleep interval) and more variable. In addition, the non-linear analysis of actigraphy registries can be used with diagnostic purposes, i.e., the diagnosis of IC may be performed without the need of medical staff. Therefore, the findings provided by actigraphy may help understand what underlies the IC as well as to make clinical trials (and the physician's daily job) swifter.

Dietetic treatments of infantile colic

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Infantile colic may be, at least in part, related to cows milk allergy, explaining why different elimination diets have attempted. A meta-analysis (Lucassen PL et al, 1998) showed the efficacy of replacing cows milk by a soy formula in 25% of infants and by a casein hydrolysate-based formula in 22% of infants, without any side-effect. The meta-analysis did not evidence any efficacy of a lactose free formula and a trial did not show any the efficacy of a soy formula versus dicyclomine (Oggero R et al, 1994). An open trial tested the efficacy of a casein hydrolysate-based formula compared to dicyclomine: 42% of infants were crying less than 1 hr / day after 2 days of treatment, with a remission persisting at 1 month (Oggero R et al, 1994). Two trials confirmed the efficacy of a hypoallergenic formula, using a whey protein (and not a casein) hydrolysate. One showed a decrease in crying duration, 101 min / day after 1 week of treatment (Lucassen PL et al, 2000). The other one, with a high proportion of infants dropped out after randomisation, showed a decrease of 1.5 colicky episode / day after 2 weeks of treatment (Savino F et al, 2006). Another trial with a hydrolysed formula but no indication as to the type of protein hydrolysate used showed a decrease in crying duration of 128 min / day (Arikan D et al, 2008). Recently a controlled trial with an alpha-lactalbumin enriched and probiotic-supplemented infant formula in infants with colic did not evidence any significant effect on colic but an improved gastrointestinal tolerance (Dupont C et al, 2010). In breastfed infants, an open Australian trial showed that mother feeding with a hypoallergenic diet, excluding cows milk and the major food allergens (egg, peanuts, tree nuts, wheat, soy, fish) was associated with a 25% decrease in crying duration in 1/3 of infants (Hill DJ et al, 2005).

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Severe infantile colic and diet

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Infantile colic is an extremely frequent problem. Its incidence varies between 20 and 48 % using this definition: "children crying more than 3 hours/day for at least 3 days/wk". Colics are present at a well known hour in later afternoon and in the first hours of the night.
The symptoms begin before the 6th week after birth in 90% of patients and almost 50% of children improve at the end of the third month and fully recover after the 6th month. The fits of crying are often accompanied by swelling of the abdomen due to intestinal gas, regurgitation and sleep disturbances. The causes of infantile colic are still unknown even today.

Both psycho-social factors and disturbances in the mother-child relationship seem to play a role in its pathogenesis but this has not been definitely demonstrated. Other pathogenetical factors are considered to be hormone levels in the blood, reduction of intestinal disaccharidases, alteration of intestinal micro-flora or alimentary hypersensitivity.

In 1921 Shannon observed that infants with colics who were breast-fed overcame their symptoms when particular foods were eliminated from their mothers' diet. The same data were confirmed by Lyndberg more recently.

In our experience infantile colic seems to be related to cow's milk protein allergy (CMPA). To determine the relationship between infantile colic and CMPA in formula-fed infants 70 (38 male) pts. were selected, with mean age 30.2 +/- 21.4 days, with severe colic (duration of crying >4h per day for 5 days per week). In 50 of the infants in the study group (71.4%) there was a remission of symptoms when cow's milk protein was eliminated from the diet. Two successive challenges caused the return of the symptoms in all of these 50 infants. There was a positive anamnesis for atopy in 9 out of 50 of patients

with CMPA-related colic and in 1 out of 20 of those with non-CMPA-related colic($p>0.05$).

A follow-up period of 18 months' mean duration showed that 22 out of 50 (44%) of the infants with CMPA-related colic and 1 out of 20 (5%) of the infants with non-related colic developed an overt alimentary intolerance ($p<0.02$).

In conclusion, when facing a formula–fed infant with severe colic, it can be affirmed that CMPA can be a cause of this symptom after having ruled out organic disease by some simple exams such as fecal blood test and/or calprotectin fecal test and/or urine test.

Consequently, a change in formula and the introduction of a CMPA-free diet should be the first and most rational medical intervention in these infants.

Finally, the well-documented possibility that infants will develop other alimentary intolerances with various types of clinical manifestations at a later age underlines the necessity of a careful alimentary follow-up.

Associations between problems with crying, sleeping, and / or feeding in infancy and long–term behavioural outcomes in childhood

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Background: Early regulatory problems (RP), i.e., excessive crying, feeding, and sleeping difficulties, have been reported to be predictors of cognitive and attention-deficit/hyperactivity problems. However, previous studies had limitations such as small sample size or retrospective design.
Aim: To investigate whether persistent RP from infancy until preschool age are precursors of attention-deficit/hyperactivity problems and cognitive deficits at school age.
Study design: A prospective study from birth to 8.5 years of age.
Subjects: 1120 infants born at risk.
Measures: RP were assessed at 5 months (i.e., excessive crying, feeding, and sleeping problems), 20, and 56 months (i.e., eating and sleeping problems) via parent interviews and neurological examination. Attention-deficit/hyperactivity problems and IQ were assessed by standard tests, direct observations in the test situations, and parent interviews at 8.5 years of age.
Results: 23.8% of the sample born at risk had RP at least at two measurement points until preschool age. Persistent RP predicted lower IQ (β=-.17; 95% CI (-.21; -.10)), behaviour problems (β=-.10; 95% CI (-.15; -.03)), attention (OR 2.43; 95% CI (1.16; 5.09)) and hyperactivity problems (OR 3.10; 95% CI (1.29; 7.48)), and an ADHD diagnosis (OR 3.32; 95% CI (1.23; 8.98)) at school age, even when controlled for psychosocial and neurological confounders.
Conclusions: Early persistent RP increased the odds of ADHD and associated problems at school age, indicating a cascade model of development, i.e., infant behaviour problems provide the starting point of a trajectory of dysregulation through time.

Infantile colic: lessons from systematic reviews

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In this presentation, Professor Macdonald will introduce participants to the challenges of synthesising the evidence about the effectiveness of interventions used to prevent or ameliorate infantile colic. She will highlight some key weaknesses in the present evidence-base, describe the reviews completed and currently under way within the Cochrane Collaboration, and suggest some ways in which primary research could be strenghtened.

Multiple systematic reviews: methods for assessing discordances of results - infantile colic case

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The process of systematically reviewing research evidence is useful for collecting, assessing and summarizing results from multiple studies planned to answer the same clinical question. The term "systematic" implies that the process, besides being organized and complete, is transparent and fully reported to allow other independent researchers to replicate the results, and therefore come to the same conclusions. Hundreds of new systematic reviews are indexed every year. The growing number of systematic reviews exploring the effects of interventions for infantile colic increases the likelihood of finding multiple and discordant results.

OBJECTIVES:
To explore the impact of multiple and discordant systematic reviews assessing interventions for infantile colic: (a) if it is likely that different systematic reviews on this topic give different results or conclusions; (b) which methods or interpretation characteristics can explain the differences in results or conclusions.

METHODS:
This presentation outlines some methods used to explore the frequency and the causes of discordance among multiple systematic reviews on the same topic. Cochrane reviews are compared to non-Cochrane reviews. Infantile colic is the case study.

CONCLUSION:
This aim is particularly relevant for both clinicians and care givers. Judgments about evidence and recommendations in health care are complex, and might face situation of discordant results.

Atopy, gut microflora and probiotics

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The prevalence of atopic diseases including food allergy, atopic eczema, allergic rhinoconjunctivitis and asthma has considerably increased during the past decades. This increase has occurred simultaneously with lifestyle-related changes in microbial contact in developed countries. Epidemiological findings showing an association between aberrant gut microbiota composition in early infancy and subsequent development of atopic disease was the initial stimulus to investigate whether the risk of eczema in infants might be reduced by probiotics, i.e. live or inactivated microbes which, when consumed in adequate amounts, confer health benefits.

Several clinical trials have demonstrated that early probiotic intervention significantly reduces the risk of developing eczema in high-risk infants. Interestingly, the protective effect seems to extend into childhood. However, there are also reports of studies with negative results. These discrepancies may be explained by differences in probiotic strains used, the population studied and the timing and duration of probiotic supplementation.

It appears that probiotic intervention is more effective if commenced already during pregnancy through the mother. We have recently provided data to suggest that strictly maternal probiotic supplementation during the last 2 months of pregnancy and the first 2 months of breastfeeding significantly reduces the risk of atopic eczema in the infant during the first 2 years of life. There are data to suggest that maternal probiotic intervention modulates innate immune gene expression in the placenta and in the fetal gut. After birth, maternal probiotic supplementation increases the concentration of TGF-β2, a tolerogenic cytokine, in breast milk. These data indicate that maternal probiotic supplementation exerts its effect on the fetus and the infant via indirect, hitherto poorly understood mechanisms.

Maternal probiotic supplementation may prove to be a safe and effective means of improving infant health.

New treatments for Infantile colic

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Introduction: Infantile colic is a common condition worldwide: about one in five infants younger than three months develops colic. Although infantile colic is considered to be a self limiting and benign affection, it is often a stressful problem for parents and a frequent and wrongly undervalued cause for pediatric consultation. Infantile colic is defined as episodes of inconsolable crying in an otherwise healthy infant younger than three months of age, that last at least three hours a day and occur at least three days per week over the course of at least three weeks in a month, a definition first proposed by Wessel (1954). According the more recent definition by Hyman (2006), colicky infants cry constantly during the evening at about the same time each day on at least one week, but they are otherwise healthy.
Other signs frequently associated to inconsolable crying are flushing, abdominal distension and leg contracture. In addition, changes to the crying sounds (higher pitch), burping, needing to eat, difficulty with passing stools, tight fists, kicking, arching the back and other manifestation of pain are reported in literature. Fortunately, infantile colic is not meant to last long: it usually begins at about two weeks of age and improves by the fourth month.

Diagnosis: The diagnosis is easy getting an exhaustive anamnesis and performing a correct physical examination in order to evaluating signs and symptoms. Other underlying serious diseases and feeding disorders must be excluded. A careful anamnesis has to include the relationship between infant's behavior and the episodes of crying, time of day and duration of them. A complete physical examination should be performed by pediatrician. It is important to evaluate if the infant is correctly fed, is gaining weight, has diarrhea, fever or unusual

stools. Additional signs and symptoms such as eczema or diarrhea should be elicited as these may be suggestive of a common condition such as cow's milk protein allergy. Also gastro-oesophageal reflux or more uncommon but life-threatening causes such as bowel intussusception have to be evaluated. A negative physical examination in an infant showing paroxysmal and inconsolable crying indicate no need for biochemical and radiological examination.

Etiopathogenesis: Despite the prevalence of the condition, the pathogenesis remains mainly misunderstood. A theory hypnotizes that infant's nervous or digestive system may be immature. Also behavioral issues such as family tension or inadequate interaction between parents and infant have been considered, but these issues are really controversial. Concomitant risk factors remain partially unknown; however, maternal smoking, increased maternal age and firstborn status may be associated to the development of infantile colic.
Recently a low amount of lactobacilli and an increased amount of coliform bacteria in the intestinal microbiota have been reported as a possible cause of gut dysmotility and increasing of gas production. In infants affected by colic were found higher levels of ghrelin and motilin, even though further studies are required to clarify their role in infantile colic. As a consequence of the lack of a complete comprehension of the causes of the condition, a wide spectrum of treatment modalities has been suggested.

Treatments:

- Dietary advices for breast-fed infants: a monitored low allergen maternal diet avoiding cow's milk and dairy food with appropriate intake of vitamins and minerals may be suggested. A period of at least two weeks is necessary to check the effectiveness of the diet and dietary intervention in mother have to be continued only if effective.
- Bottle-fed infants: first-line approach is represented by formulas based on partially hydrolyzed whey proteins with prebiotic oligosaccharides and probiotics, that have been tested

to be effective. Extensively hydrolyzed formulas based on casein or whey could be useful in children with severe infantile colic or additional atopic symptoms. However, it is crucial that any dietary changes or therapies are performed only under the supervision of the pediatrician.

- Pharmacological treatments: Simethicone, which reduces gas production, may be helpful for some infants, although several randomized controlled trials noted no difference in reducing colic episodes compared with placebo. A RCT evaluated the use of a symptomatic anticholinergic agent, cimetropium bromide, in reducing crying during colic episodes in breast-fed infants. Current literature does not recommend the use of any other drugs because of reported side effects. A new pharmacological agent (Nepadutant) acting on intestinal motility and sensitivity is under investigation with a multi-centre, multinational, randomized, double-blind, placebo controlled study at phase IIa (ClinicalTrials.gov Identifier: NCT01258153).

  A Cochrane Review on pain relieving agents is in progress.
- Probiotics: the use of probiotics in infantile colic is based upon the hypothesis that aberrant intestinal microflora could cause gut dysfunction and gas production, contributing to symptoms. Some studies have shown that administration of *Lactobacillus reuteri* ATCC 55730 and its daughter strain *Lactobacillus reuteri* DSM 17938 to breastfed infants is well tolerated and improves symptoms of infantile colic compared with placebo. This effect may be related to induced changes in the fecal microbiota, in particular a reduction of *E. coli* colonization has been observed. At present, growing data are available on the role of probiotics in colic, but there is a great interest within medical research in the understanding of the mechanisms by which probiotic bacterial strains antagonize pathogenic gastrointestinal microorganisms or exert other beneficial effects in vivo.
- Complementary and Alternative Therapies: in the absence of safe and effective pharmacological interventions,

complementary therapies have assumed an increasingly important role in the management of infantile colic.

- Herbal supplements: herbs such as fennel (*Foeniculum vulgare*), chamomile (*Matricariae recutita*) and lemon balm (*Melissa officinalis)* may help calming the infant and reducing abdominal distension. However, the administration of herbal products in infants with colic raises some concerns about the potential nutritional effects (these treatments provided for a long time could lead to a decreased intake of milk), the lack of standard dosages and the possible content of sugar and alcohol. In conclusion, parents have to use them with attention and under medical control.
- Manipulative therapies: Cochrane Database Systematic Reviews and randomized trials published in last years focused on this kind of intervention for infantile colic. Chiropractic treatment may offer short-term relief (reduction of daily hours of crying compared with no treatment or placebo), but long-term benefits are not demonstrated. The controversial nature of these interventions, their popularity among caregivers and the presence of weak supportive evidence underline how further rigorous researches are needed.
- Acupuncture: standardized light stimulation of the acupuncture point LI4 twice a week for 3 weeks has shown reduction in the duration and intensity of crying, with no serious reported side effects. Future researches are needed to validate the results and to investigate the efficacy of other acupuncture points and modes of stimulation for the treatment of infantile colic.
- Behavioral interventions: parents' responsiveness should be stimulated but with recommendations not to exhaust themselves and underlying that they can leave their infant with others when necessary. Many studies have proposed "infant massage", although it does not significantly improve symptoms. A recent Cochrane

Database Systematic Review acknowledges that “there is some evidence of benefits on mother–infant interaction, sleeping and crying, and on hormones influencing stress levels. Further research is needed”. A more recent study describes an approach based on regularity in infant's daily care and feeding, accompanied by instructions to swaddle during sleep. The aim consists in helping the infant to establish a regular sleep–wake rhythm that can reduce parental distress and improve quality of interaction between parents and child.

Conclusions: the first step is to exclude other possible causes of inconsolable crying. When the diagnosis of infant colic is confirmed, the pediatrician has to provide parents with reassurance and offer general advice, emphasizing the favourable and self-limiting nature of the condition. In the meantime a well-tolerated, multifactorial and personalized strategy should be adopted in order to provide safe and effective therapeutic approach.
Good-quality studies are needed to develop specific clinical guidelines to help pediatricians in the management of infantile colic.

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