Infantile colic as the clinical expression of brainstem dysregulation: a narrative review

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ABSTRACT

Despite many years of research, the cause of infantile colic is as elusive as ever and no distinct cure has emerged. Evidence is reviewed that colic may be the clinical expression of physiological dysregulation at the brainstem level, particularly of the vestibular and autonomic systems. It is argued that occipital/upper-cervical muscular tightness acquired at birth may induce aberrant proprioceptive flow into the vestibular system and, indirectly, the medial cerebellar cortex. Diminished inhibitory modulation of the vestibular nuclei by the medial cerebellum may provide a mechanism of how vestibular dysregulation/ hyperactivity may arise and subsequently be propagated downstream to also involve the autonomic systems. Treatment aimed at relaxation of tight sub-occipital musculature may restore regular proprioceptive flow and facilitate normalization of the inhibitory cerebellar modulation of the vestibular nuclei. From an evolutionary perspective the high prevalence of infantile colic may be an inherent aspect of the human condition and may be the price we pay for our upright stance, bipedal gait and difficult birth process as compared to the great apes. The focus of future research should be broadened to include the concomitant symptoms of colic that point to brainstem involvement.

Key Words: Infantile colic, brainstem dysregulation, sub-occipital dysfunction, proprioception, sensory neuromodulation, vestibular, autonomic.

Introduction

With an estimated prevalence of 15-25% infantile colic is one of the commonest early childhood afflictions, along with Functional Gastro-Intestinal Disorders (FGID)[1,2] Still, colic remains enigmatic. To date, 68 years after the rule-of-three diagnostic criteria were formulated[3] and after a great deal of research, the cause of colic is as elusive as ever and no distinct cure has emerged. In the intervening years much research has been focused on the crying per se and on establishing if and how colicky crying differs from normal crying[2,4] In addition, a multitude of possible contributing factors, pathological and non-pathological, have been proposed, often in a rather haphazard fashion. These include dietary causes such as cow's milk or fructose intolerance, GER(D), (neuro)developmental problems, behavioral problems, difficult temperament, transient hyperresponsivity, immaturity of the gut, gut dysbiosis, over/ underfeeding, imbalance of the autonomic nervous system, high levels of distress.[5,6,7] Organic pathology is rarely present.[8] Several authors have suggested that colic is just the extreme end of a spectrum of normal crying behavior,[9,10] although this is unlikely from an evolutionary as well as an energy perspective.[11] Others pointed to the dynamics of infant-parent interaction.[12] This is also unlikely as it cannot account for those cases where one baby of a pair of twins is colicky whereas the other is not.[11] In recent years a close association with childhood/adolescent migraine has become apparent whose significance, however, is still uncertain.[13]

After all these years, the diagnosis is still one of exclusion, being based upon excess crying in the absence of a recognizable cause. This puzzling lack of progress may suggest one of two possibilities, either colic is such an intractably difficult problem that 68 years was simply too short an interval for a solution to be found, or the research effort may have been misdirected.

From a biological perspective, small infants are primitive creatures who still function at a very basic level of visceral brainstem reflexes, because higher inhibitory modulating structures are not sufficiently developed yet.[14,15] This implies that any behavioral or physiological dysregulation observed may reasonably be expected to arise from this same level. Yet, the possibility that infantile colic could reflect a dysregulation at the brainstem level has received scant attention.

In a recent study conducted in my clinic, a 5-point clinical index of vestibular (hyper)activity was presented and applied as a tool to evaluate brainstem dysregulation in colicky babies before and after gentle treatment compared to non-colicky babies (see information box next page).[11] Colicky babies, it appears, are not just babies who cry a lot. They also show clinical evidence of vestibular dysregulation i.e., dysregulation at the brainstem level. Before treatment, the vestibular index was 7.8 times higher for colicky than non-colicky babies. Following treatment, the index had decreased by 96.5%, signifying a normalization of vestibular regulation.

In this review, relationships between infantile colic and

brainstem dysregulation are further investigated, as is the role of upper-cervical muscular dysfunction acquired at birth.

Colic and brainstem dysregulation

As one of the first sensory systems to emerge in the embryological development of vertebrates, the vestibular nuclei have extensive projections to other brainstem nuclei and play a central role in many regulatory processes.[16,17] This means that any vestibular dysregulation present may be propagated downstream to also involve these other brainstem nuclei, particularly those of the autonomic and the trigeminal systems.[18,19] Indeed, from scattered sources throughout the literature, supportive evidence of brainstem dysregulation in infantile colic can be gleaned. Though little studied, concomitant symptoms that are commonly associated with colic include (1) asymmetric posture (C-curve) and head preference even while asleep, which may lead to developmental plagio/brachiocephaly;[20] (2) extensor hypertonicity and pseudo-opisthotonic posture;[20,21] (3) upper-cervical movement/joint dysfunction, muscular tightness and occipital tenderness;[20] (4) high levels of stress and stress arousal;[9,21,22] (5) (breast)feeding difficulties;[23-26] (6) gastro-intestinal regulatory disorders such as regurgitation /Ger(d) and intestinal cramps.[1]

Extensor posture

Relaxed, happy babies have a snug, flexion-dominated fetal posture.[14] Their necks are wobbly and when held upright against the parent's chest the head needs to be supported. In stark contrast colicky babies are extension-dominated and arch their back.[20] Parents must be alert not to let the baby slip from their hands (back dive). These babies are noted to have a "strong neck," a "strong back" and "strong legs" and, when held in front, they try to climb up against the parent's chest. When placed in a prone position, they tend to lift their head, pull up their legs and try to move forward in a froglike fashion, even as early as the first few days after birth. Because in young infants, extensor posture and hypertonicity point to activation of anti-gravity muscles by the vestibulo-spinal tracts, the observed postural characteristics (1,2,3) are suggestive of vestibulo-spinal hyperactivity.[15,16,27]

The clinical index is based upon the consideration that mild rhythmic stimulation has a relaxing, soothing effect, whereas overstimulation tends to be uncomfortable and may lead to dizziness, nausea or even vomiting. If a baby does not react well to mild vestibular stimulation this is taken as a possible sign of vestibular (hyper)activity. The clinical index is comprised of five statements each of which can be answered by a simple agree/disagree. Each "agree" earns one point and each "disagree" earns zero points. These statements are based upon literature reports, personal observations and reported parental experiences:

(A). Your baby does not calm down or fall asleep during a car ride.

(B). Your baby does not calm down or fall asleep when held against your chest or cradled in the crook of your arm, while walking around at a brisk pace.

(C). When your baby has fallen asleep against your chest you cannot lay the baby supine in the crib without the baby waking up and crying.

(D). When sleeping the baby may wake up with a scream, showing the symptoms of the Moro reflex.

(E). The baby is much more comfortable lying inclined in a car seat than supine in a crib.

Information box 1: 5-point clinical index of vestibular (hyper) activity (reference 11)

Stress characteristics

Colicky babies are restless, irritable, in obvious distress, have trouble falling asleep and have fragmented sleep patterns (15-20 minute cat naps), they scratch their face, are easily startled, react strongly to minor sensory stimuli (hyperreactivity, hyperarousal, hypervigilance) and are easily overstimulated.[21] In addition, they tend to have cold clammy hands and feet. Together these symptoms point to sympathetic activation, as do the shrill and high-pitched acoustic characteristics of colicky crying.[22,25,28-33] Studies of covariation of infant cry acoustics and autonomic state have shown that the pitch of infant cries and other aspects of vocal prosody provide a sensitive index of autonomic activity.[34] Less vagal output is associated with increased pitch, whereas increased vagal output is accompanied by a lowering of pitch. Shrill high frequency cries indicate distress reflecting decreased vagal output or increased sympathetic activation. In a recent development a mobile telephone app ("Chatterbaby") incorporating a cry-translation algorithm allowed discrimination of cries associated with fussiness, hunger, pain and colic with 70-90% accuracy.[35] It was found that the cries of colic were similar to those of pain, but of higher intensity and pitch, suggesting that colic may be painful and stressful. Another study reported that increased levels of salivary cortisol in colicky babies were related to fragmented sleep patterns and intensity of crying, suggesting activation of the HPA-stress system.[36] Actually, the sympatico-adrenomedullary (SAM) and the hypothalamic-pituitary-adrenocortical (HPA) stress systems may both be activated.[24]

Feeding problems

Co-occurrences between infantile colic and feeding problems are reported, but interrelationships have been little studied. In hospital-admitted colicky babies, feeding problems were twice as common as in non-colicky babies.[24] In a different study colicky babies had (i) more gastro-esophageal reflux (GER); (ii) were less responsive during feeding interaction with the mother; (iii) had more episodes of feeding discomfort and (iv) had greater difficulty

coordinating sucking, swallowing and breathing.[23] This led the authors to suggest that colic and feeding problems could both be related to some underlying disorder of behavioral dysregulation. An association between feeding problems and colic was also reported in a study that looked at suck-swallow-breathing-coordination (SSBC) in colicky and non-colicky babies.[26] The authors observed that the duration of feeding in colicky babies was twice the normal 15-20 minutes in non-colicky babies. In addition, colicky babies showed dysfunctional relationships for elements of SSBC, similar to but more subtle than those observed in infants with neurological difficulties. Though in colicky babies there is no evidence of neurological deficit, the feeding difficulties could still reflect a dysregulation of brainstem autonomic nuclei, because sucking, swallowing, breathing and vocalization are coordinated by the nucleus ambiguus of the vagus system.[28,37]

Gastro-intestinal problems

In small infants, gastro-intestinal disorders including regurgitation (gastro-esophageal reflux, GER) constipation and intestinal cramps with or without obstipation or dyschezia are common in association with colic.[1,38] Frequent associations are gas/bloating/colic, gas/bloating/regurgitation and regurgitation/colic. These symptoms have been interpreted as early manifestations of later childhood painful FGID's.[39-41] Regurgitation (Ger) involves a transient relaxation of the lower esophageal sphincter triggered by gastric stretch receptors and not by passive mechanical distension of the gastro-esophageal junction.[42,43] This may indicate that excessive regurgitation could reflect dysregulation of autonomic neural control. Alternatively, the infants could just be nauseous due to dysregulation and hyperactivity of the vestibular system.[11,19] In case of constipation the presence of dry hard stools may suggest decreased gut motility due to decreased parasympathetic output or sympathetic activation and point to autonomic dysregulation.[44] Infant dyschezia is defined as excessive straining for more than 10-20 minutes with or without passing of stools[1] and is thought to be due to failure to coordinate intra-abdominal pressure with relaxation of the muscles of the pelvic floor.[45] Again, this may point to dysregulation of autonomic neural control.

Colic, upper-cervical dysfunction and mild birth trauma

Scattered evidence suggests that the origin of the upper-cervical muscular dysfunction and occipital tenderness may be related to the birthing process. One study documented an association between colic and feeding problems and found that the main risk factor was a complicated pregnancy or birth process.[24] Another study reported that breast feeding problems were more common following assisted births than non-assisted births.[46] Stressed and difficult temperamental behavior apparently are already present during the first few days after birth,[47] and high responsivity (stressed) behavior during the first week was predictive of colicky behavior during the following weeks.[48] A recent MRI study revealed that already shortly after birth "colicky babies showed greater sensitivity to olfactory stimuli than their non-colicky peers."[49]

Biedermann[20] was the first to have specifically linked upper-cervical dysfunction and colic to mild birth trauma related to the difficult human birth process as compared to the great apes. In the course of human evolution, the development of bipedal locomotion and the concomitant adaptation of the pelvic architecture preceded the increase in brain size by several million years.[50] In modern humans there is a very tight fit between the size of the baby and the maternal birth canal leaving only a small margin of error. As a result, the human baby must negotiate a narrow and tortuous birth canal[51-53] leading to a high level of birth complications with mother and child in comparison to the great apes.[54] During birth the skull is subjected to molding forces while the neck undergoes a considerable degree of rotation and extension.[55,56] It is easy to envisage how in a percentage of births such twisting may result in upper-cervical movement and joint dysfunction, muscular tightness and tenderness,[20] particularly in view of the observation that small meningeal bleeds are common even in non-symptomatic neonates.[57,58] In most births the final exit turn is to the right, and, accordingly, if there is a distinct head preference, in 70-80% of cases this is also to the right.[59] In chimpanzees with their easier birth process inconsolable crying as in human colicky babies is unknown.[60] Although infant chimps cry, they stop crying as soon as they are handled by the mother.

Colic, brainstem dysregulation and upper-cervical dysfunction

How these entities are interlinked may be inferred from the realization that upper-cervical proprioception plays

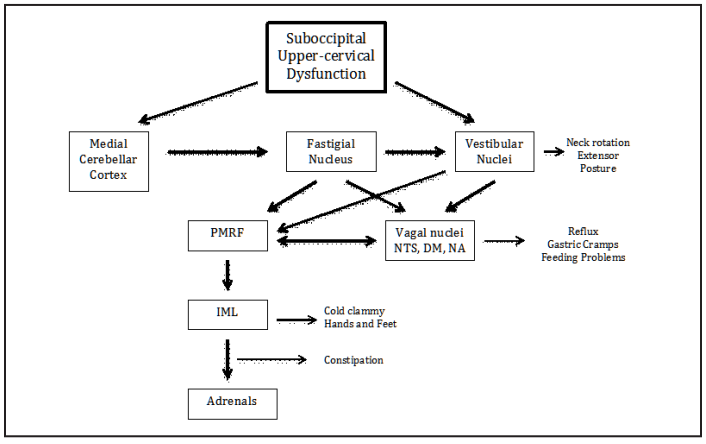

Figure 1: Functional relationships of sub-occipital musculature, medial cerebellar nuclei, vestibular nuclei, reticular formation, vagal nuclei and adrenals. PMRF — pontomedullary reticular formation; NTS — nucleus tractus solitarius; DM — dorsal motor nucleus; NA-nucleus ambiguus; IML — intermediolateral cell column.

an important role in modulating the vestibular system, as does the visual system.[61-63] Afferent proprioceptive input from upper-cervical segments (C1-3) and from axial structures project to the vestibular nuclei and indirectly to the medial cerebellar cortex and its purkinje cells and from there to the fastigial nucleus, which is the output nucleus of the medial cerebellum (Figure 1).[16] By inhibition of the fastigial nucleus the purkinje cells of the medial cerebellum indirectly exert an inhibitory modulating influence on the vestibular system.[16,19,27,64] Vestibular hyperactivity may arise even in case of weak, subclinical, diminished cerebellar inhibition.[19,65] Consequently, aberrant proprioceptive traffic into the vestibular system and the medial cerebellum, arising from tight sub-occipital musculature acquired at birth could conceivably lead to dysregulation and hyperactivity of the vestibular nuclei. Conversely, treatment achieving relaxation of the tight musculature may be expected to restore regular proprioceptive flow and facilitate normalization of the inhibitory cerebellar modulation of the vestibular nuclei.

Young infants in particular may be vulnerable to vestibular dysregulation, because compensation via the visual system would not be available as visual gaze and the vestibulo-ocular reflex (VOR) remain to be fully established.[15] In small babies, vestibular modulation may be almost entirely dependent on upper-cervical proprioception. The vestibular and the fastigial nuclei send efferent projections to the autonomic nuclei and to the reticular formation, and from the latter onwards to the sympathetic chain and the adrenal glands (Figure 1).[16,66,67] This means that dysregulation of the vestibular nuclei may propagate along these projections to also induce dysregulation of the sympathetic and parasympathetic systems, such as inferred in the above review of concomitant symptoms.

Colic and childhood/adolescent migraine

Although a close association between colic and migraine seems well established,[13,68-70] the discussion of its significance is hampered by the fact that there is no generally agreed pathophysiological model for either of these disorders. Some authors have suggested that colic and migraine may share a common pathogenic mechanism such as excessive sensitivity to sensory stimuli[71] or increased sensitization of perivascular nerve endings in the meninges and the gut,[13] possibly mediated by calcitonin-gene-related peptide (CGRP). At least one case-control study found an association between migraine and functional gastro-intestinal disorders in children and adolescents.[72] Circadian rhythms have also been suggested as being at the base of both colic and migraine.[71] Other authors have suggested that there may be a continuum from colic, as the earliest manifestation of migraine, through other childhood precursors of migraine, to migraine in adolescents and adults.[73]

Discussion

It is proposed that in a percentage of births the human baby may suffer mild trauma, as initially suggested by Biedermann,[20] and that this may have far reaching effects.[11] The associated muscular tightness and accompanying movement/joint dysfunction may have an adverse effect on the vestibular and autonomic systems of the brainstem. Via a mechanism of aberrant proprioception, this may lead to dysregulation/ hyperactivity of the vestibular nuclei and the ensuing concomitant autonomic symptoms of colic. Such a mechanism may explain why in many babies the full spectrum of colicky behavior is not reached until several weeks after birth.[9,10] The finding of a 96.5% improvement of the vestibular index following treatment consisting of mild sensory stimulation[11] is consistent with restoration of regular proprioceptive flow and normalization of vestibular modulation by the medial cerebellum. It would suggest that central neuromodulation may be accomplished not only by cutaneous vibratory stimulation of the cymba of the external ear (sensory neuromodulation),[74] but also by similar proprioceptive stimulation of the sub-occipital musculature, at least in babies.[11] The spontaneous resolution of colicky behavior after 3-5 months may be a consequence of developing cortical control and inhibitory modulation of brainstem reflexes during this same period and may, thus, represent a developmental aspect of the disorder.[15,37]

However, this is not to say that in untreated babies the underlying dysfunction also resolves in all cases as there is accumulating evidence of longtime sequelae.[75,76] In a 10-year prospective study an association was found between infantile colic and recurrent abdominal pain, allergic disorders, sleep disorders, fussiness, aggressiveness.[77] A second study found that at three years of age former colicky babies had more sleeping problems and more frequent temper tantrums than former non-colicky babies. Also, families with colicky babies had more distress three years later.[76] In a third study ex-colicky babies at four years of age were more emotional and had more temper tantrums and more complaints of stomachache.[78] Infantile colic has also been linked to an increased risk of Irritable-Bowel-Syndrome (IBS) after four years of age.[41] By contrast, treated colicky babies three years later were less likely to experience long-term sequelae than colicky babies who had not been treated.[79]

As to the nature of the link between infantile colic and migraine, there is a tendency to not only consider colic as the earliest age-specific manifestation of migraine, but also implicitly equate colic with early migraine.[70,73] Some authors even went so far as to suggest that migraine medication could be useful in controlling colic.[68] The relationship, however, cannot be that straightforward, because the great majority of colicky babies do not develop migraine.

If colic is to be an early manifestation of migraine, this

would probably only apply to a minority of genetically predisposed individuals. In the only available cohort study, 23% of ex-colicky babies developed migraine, 77% did not and of the ex-non-colicky babies 11% still did.[80] From twin studies it is estimated that 30-60% of migraine cases are accounted for by genetics, which leaves a remaining 70-40% to non-genetic external and environmental factors.[81] If, as argued in this review, babies' function at the basic level of visceral reflexes and if infantile colic is the clinical expression of brainstem dysregulation, it would stand to reason that the link with childhood migraine should also be sought at this level. Speculatively, and from an evolutionary perspective, the high 15-25% prevalence of infantile colic may be an inherent aspect of the human condition and could be part of the price we pay for our upright stance, bipedal gait, and the difficult way we are born.

Future research

Given that after all those years the diagnosis of infantile colic is still one of exclusion, it is paramount that criteria be developed for a diagnosis based on distinct and objective clinical observations. A first step towards this end has been made by the earlier study conducted in my clinic in which a 5-point clinical index of vestibular hyperactivity was presented and applied to evaluate brainstem dysregulation in colicky babies before and after treatment versus non-colicky babies.[11] This index offers the prospect for development into a tool for a positive diagnosis. The recognition of the various concomitant symptoms reviewed above allows additional clinical indices to be developed i.e., postural index, stress index, index of feeding behavior, regurgitation index, index of gastric cramps. Once confirmed and validated, these indices together with the vestibular index may be integrated into a comprehensive instrument toward an objective and practical clinical diagnosis of infantile colic. It is suggested that the focus of future research should be broadened to also include the associated symptoms that are indicative of brainstem dysregulation. Also, the link with childhood/adolescent migraine should be further explored.

Conclusion

Colicky babies are much more than just infants who cry a lot. They also show clinical evidence of dysregulation at the brainstem level, particularly of the vestibular and autonomic nuclei. As a hypothesis it is proposed that colicky behavior, vestibular dysregulation and concomitant autonomic dysregulation are linked to sub-occipital/ upper-cervical muscular dysfunction secondary to mild birth trauma. Treatment aimed at relaxing tight sub-occipital/ upper-cervical musculature (sensory neuromodulation) may correct aberrant proprioceptive outflow to the vestibular nuclei and the medial cerebellum. This may facilitate normalization of vestibular inhibitory modulation by the cerebellum and lead to improvement of brainstem regulation. It would suggest that central neuromodulation can be effectuated, not only by vibratory sensory stimulation of the auricular branch of the vagus nerve, but also by similar proprioceptive stimulation of sub-occipital/upper-cervical muscular structures, at least in babies.

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