Hay fever is associated with prevalence, age of onset and persistence of stuttering

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Abstract

Objectives Atopic diseases and adverse childhood experiences are associated with neurodevelopmental disorders including developmental stuttering. This study examined the associations between these factors and lifetime prevalence, age of onset and persistence of developmental stuttering.

Methods Data from 4,874 participants (2264 men and 2610 women) from the PsyCoLaus study were used. Prevalence, age of onset and persistence of stuttering were investigated through univariate, bivariate and regression analyses.

Results Regression analyses indicated that hay fever, gender, familial aggregation and fear of punishment by parents, were associated with stuttering onset in childhood with odds ratios (OR) of 2-3. Hay fever was associated with an earlier onset of stuttering (difference of 1.5 years, p=.001). Moreover, early onset of stuttering (OR=0.8, p=.009) and hay fever (OR=9.2, p=.002) predicted whether stuttering persisted.

Conclusions This study suggests that immunological imbalances related to atopic diseases such as hay fever and adverse childhood experiences are also related to stuttering. The importance of this link is emphasized by the fact that hay fever is also associated with age of onset and persistence of stuttering.

Running title: Hay fever and persistence of stuttering

Key words: stuttering, age at onset, persistence, hay fever, adverse childhood experiences

Developmental stuttering is a common neurodevelopmental disorder with a lifetime prevalence of 5-10% (Reilly et al. 2009) that has well-documented epidemiological parameters. Stuttering affects more males than females as occurs with other neurodevelopmental disorders such as attention deficit hyperactive disorder (ADHD) (Willcutt 2012), tics and the Gilles de la Tourette syndrome (Rodgers et al. 2014; Shaw and Coffey 2014). The gender-ratio (male to female) for stuttering is about 2:1 in childhood, but increases to about 4:1 in adulthood indicating that the risk for persistence is higher for males than females. However, persistence is less frequent for stuttering than is the case with other neurodevelopmental disorders (Howell 2011).

Risk factors for stuttering can be roughly divided into psychosocial factors such as impaired child-parent interactions, conflict with parents and emotional stress (Oliveira and Nogueira 2014)), familial aggregation (Reilly et al. 2009) and biological factors including prenatal/perinatal/postnatal brain damage, brain damage related to maternal alcohol consumption during pregnancy, head trauma and head injury (Ajdacic-Gross et al. 2010)). Recently, Ajdacic-Gross et al. (2018) identified atopic diseases as factors associated with stuttering which applies more generally to childhood speech disorders (Strom and Silverberg 2016a, 2016b), ADHD (Buske-Kirschbaum et al. 2013; Schans et al. 2017; Tsai et al. 2013) and other neurodevelopmental disorders. Additional evidence is accruing which shows that psychosocial stressors impact the immune system at an early age (Danese and Lewis 2017) and psychosocial stressors and the immune system impact brain development jointly at critical periods (Teicher et al. 2016).

Age of stuttering onset and whether stuttering persists have been investigated less than has stuttering incidence. Persistence of stuttering has been mainly examined in connection with speech characteristics such as severity and disorder-specific characteristics (Ambrose et al. 2015; Howell and Davis 2011; Howell et al. 2006), neural factors (Garnett et al. 2019; Kronfeld-Duenias et al. 2016; Misaghi et al. 2018; Usler and Weber-Fox 2015; Yang et al. 2016), familial aggregation (Ambrose et al. 1997) and genetics (Dworzynski et al. 2007; Kang and Drayna 2012). Other etiopathogenetic mechanisms have rarely been considered. An exception is that breastfeeding has a potential protective role with respect to persistence (Mahurin-Smith and Ambrose 2013).

In this study, we report data from a large Swiss population-based epidemiological survey, the PsyCoLaus

study. We hypothesized that atopic diseases and adverse childhood experiences are not solely associated with the lifetime prevalence of stuttering (Ajdacic-Gross et al. 2018), but also with the age of onset and the persistence of stuttering.

Method

Participants

Only required information about the PsyCoLaus study is given as full details are available elsewhere (Ajdacic-Gross et al. 2018; Preisig et al. 2009). PsyCoLaus is the psychiatric part of the population-based CoLaus|PsyCoLaus study conducted in Lausanne and comprises baseline data from N=4,874 participants (2264 men and 2610 women) aged 35-82 years.

Measures

The French version of the semi-structured Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al. 1994; Preisig et al. 1999) is the main survey instrument used in PsyCoLaus. DIGS obtains information related to common mental disorders including the course and chronology of comorbid features, somatic conditions and a range of developmental and psychosocial risk factors (Preisig et al. 2009). All information used in this study was obtained from interviews with the PsyCoLaus participants.

Stuttering was assessed by asking (in French): “Did you have problems with stuttering during your childhood?” where the responses allowed were: “Yes”, “No” or “I don’t know”. If participants answered “Yes”, they were asked at what age the stuttering had first appeared and if and when it had disappeared. Cases with a stuttering onset after the age of 12 were excluded (Ajdacic-Gross et al. 2018). Persistence of stuttering was binary coded based on whether or not it continued beyond the age of 20.

Information about potential risk factors, infectious diseases, allergies, dermatological and other somatic conditions was obtained from the medical history extension of DIGS. In this analysis, asthma and dermatitis were limited to instances with an atopic attribution. Furthermore, hay fever was dichotomized into early and

late onset (</> age of 16 which was the median reported age of onset). Family-related adverse-childhood-experiences (ACE) variables were based on answers to the following questions: 1. Did your parents fight with each other frequently? (interparental violence) 2. Did your parents ever do anything that frightened you (like lock you in a closet)? (fear of maltreatment). Moreover, traumatic experiences below the age of 10 were included in the analysis.

Familial aggregation information was assessed by the French version of the semi-structured Family History–Research Diagnostic Criteria (FH-RDC) interview (Andreasen et al. 1977; Rougemont-Buecking et al. 2008; Vandeleur et al. 2008; Vandeleur et al. 2015). Disorders in FH-RDC were divided into neurodevelopmental disorders (tic disorders, ADHD, conduct disorder, and oppositional defiant disorder) and anxiety disorders with an early onset (separation anxiety, overanxious disorder, specific phobias, social phobia). The FH-RDC information was only available for a sub-sample of 3720 of participants.

Ethics Approval

The CoLaus|PsyCoLaus study was approved by University of Lausanne's Institutional Ethics Committee (Preisig et al. 2009). All participants received a detailed description of the goals, procedures and funding of the study and signed a written informed consent form. All procedures involved in this report comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975 (2008 revision).

Data analyses

A conventional two-step approach involving bivariate and multivariate statistical analyses was used for all stuttering variables investigated (lifetime prevalence, age of onset, persistence). The multivariate (regression) analyses involved stepwise procedures in order to take account of the sample size. They were repeated by including the FH-RDC variables which was only possible for the subsample of 3720 participants mentioned above. SPSS version 23 was used for all analyses.

Results

One-hundred and eighteen participants from the PsyCoLaus sample (71 men and 47 women) reported that they stuttered as a child. The frequencies of selected associated factors and risk factors are given together with their rates (represented by proportions) in Table 1.

Table 1

More men than women reported developmental stuttering (OR 1.8, 95% CI 1.2 – 2.6)). In bivariate analyses with further risk/associated factors (Table 2), ORs for childhood adversities ranged from 1.7 (interparental violence) up to 3 (fear of parental maltreatment). Familial aggregation of neurodevelopmental and of early anxiety disorders had ORs at around 2. ORs above 2 for atopic diseases occurred for hay fever, atopic asthma and atopic dermatitis. In stepwise logistic regression analysis, gender (OR 1.9, 95% CI 1.3 – 3.0), familial aggregation of neurodevelopmental disorders (OR 2.0, 95% CI 1.2 – 3.3), hay fever (OR 2.1, 95% CI 1.4 – 3.3) and fear of parental punishment (OR 3.0, 95% CI 1.8 – 4.9) were retained in the model, whereas the effects of atopic dermatitis and trauma in childhood were dropped.

Table 2

The retrospectively reported age of onset of stuttering for those affected had mean of 5.8 years (95% CI 5.4–6.2), and median of 6 years. In bivariate analyses with adjustment for gender, only hay fever showed significant associations with age of onset (Table 3). Multivariate analyses were redundant. The onset of stuttering in those with hay fever was 1.5 years earlier than in those without hay fever (b -1.5, CI - 2.4 – -0.7, p=.001). This effect did not vary with the age of onset of hay fever which suggests that early and late onset of hay fever have similar susceptibilities.

Table 3

Persistence of stuttering was reported by 36 of the affected persons (30.8%, missing = 1), and was more frequent in men (n = 26, 37.1%) than in women (n = 10, 21.3%; OR 2.2 (95% CI 0.9 – 5.1). In bivariate

associations, persistence of stuttering was associated with earlier age of stuttering onset and earlier hay fever onset (Table 3). These two bivariate associations were maintained in multivariate analysis.

Discussion

Risk factors for developmental stuttering are similar to risk factors for other neurodevelopmental disorders including atopic diseases and adverse childhood experiences (Ajdacic-Gross et al. 2018). This study extended these findings. Fear of maltreatment by parents and hay fever, as well as risk factors such as gender and familial aggregation of neurodevelopmental disorders, were associated with developmental stuttering. Moreover, hay fever was involved both in earlier onset and, together with earlier onset, in predicting the persistence of stuttering. The multiple involvement of hay fever corroborates the need for a better understanding what the association with atopic shifts tell us about the etiopathogenesis of stuttering.

The findings of this study shed new light on the persistence issue. So far, results on persistence have been limited to selected characteristics (see above). This study is the first to suggest some exogenous – in this instance, hay fever related – risk mechanisms in stuttering are related to its persistence. Given exogenous risk mechanisms, a link in terms of physiological mechanisms is needed to explain structural and functional alterations in brain development that finally result in persistent stuttering (Chang et al. 2018a).

On a more basic level, the formal etiopathogenesis model of stuttering is open to debate. On the one hand, we could assume a single pathway of neurological dysfunction fueled by diverse mechanisms such as those associated with hay fever. According to this view, persistent stuttering would be a more severe outcome within the same pathway. On the other hand, the etiopathogenesis model could be based on several pathways which are related to different subtypes, i.e., subgroups of PWS. In this instance, persistent stuttering would be part of a subtype that is essentially different from one or several other subtypes and can also imply a more severe outcome. Multiple theoretical criteria are helpful in choosing a preliminary stance: empirical diversity of associations, complexity of the underlying biological processes and systems, heterogeneity models in comparable disorders / diseases. Basically, the more components and ‘dose’ levels , the more likely is the

multiple pathway model. Both our results and results from other groups reflect high diversity of empirical associations and involved mechanisms in stuttering.

For all neurodevelopmental disorders, it is crucial to correctly grasp the degree of heterogeneity: as this is a prerequisite for a better understanding of the condition, to instate meaningful research designs and to develop effective therapies (Smith and Weber 2017). Whilst previous work (Ajdacic-Gross et al., 2018) indicated that there are at least two pathways (subtypes, subgroups) in developmental stuttering, the current study suggested at least three pathways. Two are exogenous pathways (one related to hay-fever and one related to childhood adversities) and the third is an idiopathic pathway where the risk factors / mechanisms are not clear as yet.

Associations between atopic diseases and speech disorders have been reported previously at a general level (Strom and Silverberg 2016a, 2016b). This study narrowed the focus to hay fever, i.e., allergic rhinitis, and stuttering. Since models accounting for exogenous risk mechanisms in stuttering are absent in the main, research may draw on putative templates such as those from ADHD (Alm 2014; Healey and Reid 2003; Strom and Silverberg 2016a). The atopic diseases hay fever, asthma and eczema (Buske-Kirschbaum et al. 2013; Hak et al. 2013; Tsai et al. 2013) are factors associated with ADHD. Along with the present results, these findings imply that the etiopathogenesis of stuttering and other neurodevelopmental disorders could be related. This is further supported by unspecific symptoms that are an issue both in stuttering and in ADHD, for example, timing control (Etchell et al. 2014; Noreika et al. 2013) and other executive function deficits (Craig et al. 2016; Ntourou et al. 2018).

Since the onset age in atopic diseases, including hay fever, is usually higher than the age of onset of stuttering or ADHD, hypotheses should be focused initially on mutual underlying immune system imbalances and their consequences rather than on a direct causal relationship. One of the marked characteristics of the toddler's immune system is the shift in T helper (Th) cells, that is, of the Th1/Th2 balance towards Th2 response. This shift diminishes after the first 2-3 years as reflected by the decrease of age-specific asthma rates during early childhood (Osman 2003). At earlier ages, infections with respiratory syncytial virus (Knudson and Varga 2015), Epstein Barr virus and Cytomegalovirus (Ygberg and Nilsson

2012) help retain the basically high level of Th2 response. Another interesting detail is that breastfeeding is a protective factor in stuttering (Mahurin-Smith and Ambrose 2013), and similarly it is a protective factor in Th2-related atopic diseases (Iyengar and Walker 2012). Also, the Th2 shift is more pronounced in boys than in girls in line with the male predominance in neurodevelopmental disorders and in stuttering.

There are many reasons to focus on the role of ACE (in this analysis, represented by fear of punishment by parents) in the etiopathogenesis of stuttering. On the one hand, recurrent imagery about adverse events in childhood is more frequent in PWS then in controls (Tudor et al. 2013). Also, ACE are a particularly prominent domain in research on all other neurodevelopmental and most mental disorders. Understanding the impact of ACE in stuttering and its relation to hay fever and other atopic diseases can derive from ADHD research (Fuller-Thomson and Lewis 2015; Ostergaard et al. 2016). There is substantial evidence that ACE alters brain development (Teicher and Samson 2016; Teicher et al. 2016), and it has been convincingly argued that this is predominantly mediated by the immune system (Danese and Lewis 2017) as well as the hormonal and metabolic systems. Therefore, it seems plausible that hay fever and ACE point at different pathways. This is corroborated by the finding in this study that hay fever is involved in persisting stuttering but ACE is not.

In both instances, the exact physiological mechanisms are poorly understood. However, the general framework how these mechanisms give rise to conditions seems clear: immunological, metabolic and hormonal disturbances are able to alter the brain development by interfering with developmental processes unwinding at the current developmental age. This can result in delays and alterations of grey and white matter development, or changed network characteristics and coordination of brain networks (Smith and Weber 2017). Since the disturbances affect brain development in an unspecific way, it is not surprising that the outcomes mostly include a variety of phenotypes and comorbid conditions assignable to different and distributed brain networks. Both structural and functional outcomes have been widely documented in stuttering (Chang et al. 2018b), again in parallel to other neurodevelopmental disorders. Given that there are many parallels between these disorders, the question arises why the outcomes actually differ. A possible answer might be that the timing of any disturbance applies to a specific stage of brain development during which components of differed tasks are acquired.

Stuttering has a strategical research advantage compared to research in other neurodevelopmental disorders. Because of its idiosyncratic characteristics (narrow sensitive time window for onset, specific affected brain networks, unusual persistence rates), stuttering affords an interesting way to disentangle the specific and selective impacts of physiological disturbances during predefined stages of development of relatively well-defined brain networks. No other research domain within neurodevelopmental disorders has such privileged preconditions, and it is worth exploiting this fully in future research.

Limitations

All information from PsyCoLaus used in this study was obtained by direct interview. Thus, underreporting may result in recall bias. The participants in PsyCoLaus were aged 35–82 years at the time of first interview which reinforces recall bias regarding symptoms and other issues during childhood and adolescence. This applies not only to stuttering, but also to risk factors and other information collected retrospectively. The most obvious consequence of underreporting and misreporting is increased noise in the data and, therefore, an underestimation of effects. The choice of parameters was guided by the range of CoLaus|PsyCoLaus variables that can be linked to the early developmental stages in childhood. This range was determined by the purposes of a large and general epidemiological population based survey.

Age at onset parameters derived from surveys differ from those derived in research studies. Retrospective reports would lead to higher than the actual onset age when the time span between onset and reporting is long. This specific form of recall bias is known as a telescoping effect. Report of onset age has been critically discussed in substance use research (Bright and Soulakova 2014). Telescoping implies that a remote onset age is typically advanced on the time scale by up to 3 years. This is consistent with the later mean age of stuttering onset reported by PsyCoLaus participants compared to mean onset age derived from research studies (around 3 years). There is no evidence that telescoping regarding age of onset is biased with respect to other variables included in the present analyses.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Author contributions

VAG: drafted the analysis design, performed the data analyses, and wrote the paper. SR: collaborated with the analysis design, assisted with the data analyses and the writing. MM: assisted with the data analyses and the writing. RvK: collaborated with the study design, the analysis design and the writing. ES: collaborated with the design and the writing. EC: assisted in the PsyCoLaus study design, acquired the data and collaborated in the writing. MPFS: assisted in the PsyCoLaus study design, acquired the data and collaborated in the writing. CV: designed the PsyCoLaus study, acquired the data and collaborated in the writing. MP: designed the PsyCoLaus study and collaborated in the writing. PH: drafted the analysis design and collaborated in the writing. All authors approved the final manuscript.

Compliance with Ethical Standards

The CoLaus|PsyCoLaus study was approved by University of Lausanne's Institutional Ethics Committee (Preisig et al. 2009). All participants received a detailed description of the goals, procedures and funding of the study and signed a written informed consent form. All procedures involved in this report comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Table 1:

Selected risk/associated factors in developmental stuttering; frequencies and rates (proportions within each item)

	all		men		women	
	PwS†	Pw/oS‡	PwS	Pw/oS	PwS	Pw/oS
familial aggregation						
neurodevelopmental disorders§	18 (19.6%)	371 (11.3%)	12 (21.4%)	141 (9.3%)	6 (16.7%)	230 (13.0%)
early anxiety disorders¶	41 (44.6%)	1085 (33.0%)	21 (37.5%)	444 (29.3%)	20 (55.6%)	641 (36.2%)
interparental violence	23 (19.5%)	585 (12.4%)	11 (15.5%)	253 (11.7%)	12 (25.5%)	332 (13.1%)
fear of parental maltreatment	26 (22.0%)	438 (9.3%)	11 (15.5%)	180 (8.2%)	15 (31.9%)	258 (10.1%)
trauma below age of 10	9 (7.6%)	180 (3.8%)	3 (4.2%)	53 (2.4%)	6 (12.8%)	127 (5.0%)
hay fever	40 (33.9%)	847 (17.8%)	21 (29.6%)	399 (18.2%)	19 (40.4%)	448 (17.5%)
early onset	14 (15.2%)	304 (7.2%)	13 (20.6%)	163 (8.3%)	1 (3.4%)	141 (6.3%)
late onset	25 (24.3%)	511 (11.6%)	8 (13.8%)	217 (10.8%)	17 (37.8%)	294 (12.2%)
atopic asthma	13 (4.5%)	105 (2.3%)	7 (9.9%)	100 (4.6%)	6 (12.8%)	176 (6.9%)
atopic dermatitis	11 (4.8%)	107 (2.3%)	4 (5.6%)	68 (3.1%)	7 (14.9%)	150 (5.9%)
overall frequencies††	118	4748	71	2191	47	2557

Notes:

† PwS persons with stuttering

‡ Pw/oS persons without stuttering

§ included disorders are tic disorders, ADHD, conduct disorder, oppositional defiant disorder

¶ included disorders are separation anxiety, overanxious disorder, specific phobias, social phobia

†† missings: n=8

Table 2:

Selected potential risk factors related to lifetime prevalence of developmental stuttering: bivariate associations adjusted for sex and stepwise logistic regression analysis

	bivariate associations		stepwise logistic regression model		
	p	OR (95% CI)	Wald statistics	p	OR (95% CI)
sex	*	*	9.2	.002	1.9 (1.3 – 3.0)
familial aggregation					
neurodevelopmental disorders	.009	2.0 (1.2 – 3.4)	6.1	.013	2.0 (1.2 – 3.3)
early anxiety disorders	.012	1.7 (1.1 – 2.6)			
interparental violence	.019	1.7 (1.1 – 2.8)			
fear of parental maltreatment	.001	2.9 (1.8 – 4.5)	18.7	.001	3.0 (1.8 – 4.9)
trauma below age of 10	.014	2.4 (1.2 – 4.9)			
hay fever	.001	2.4 (1.6 – 3.5)	11.0	.001	2.1 (1.4 – 3.3)
atopic asthma	.012	2.1 (1.2 – 3.9)			
atopic dermatitis	.008	2.4 (1.2 – 4.5)			

Table 3:

Selected potential risk factors in developmental stuttering: associations related to age of onset and to persistence (adjusted for gender)

	age of onset			persistence	
	regression coefficient (95% CI)	b	p	OR (95% CI)	p
familial aggregation					
neurodevelopmental disorders	-0.0 (-1.2 – 1.3)	– 0.01	.944	1.1 (0.4 – 3.3)	.885
early anxiety disorders	0.1 (-0.8 – 1.1)	0.03	.761	1.0 (0.4 – 2.6)	.965
interparental violence	0.2 (-0.8 – 1.3)	0.04	.651	1.1 (0.4 – 3.0)	.850
fear of parental maltreatment	-0.4 (-1.4 – 0.6)	-0.07	.462	0.5 (0.2 – 1.6))	.253
trauma below age of 10	1.3 (-0.3 – 2.9)	0.15	.104	1.5 (0.3 – 6.5))	.626
hay fever	-1.5 (-2.4 – -0.7)	-0.31	.001	2.3 (1.0 – 5.5)	.051
early onset	-1.4 (-2.8 – -0.2)	-0.21	.041	9.2 (2.3 – 37.3)	.002
late onset	-1.5 (-2.6 – -0.4)	-0.28	.005	0.9 (0.3 – 2.8)	.831
atopic asthma	-0.6 (-1.9 – 0.8)	-0.08	.414	1.6 (0.5 – 5.3)	.466

atopic dermatitis	-0.2 (-1.7 – 1.3)	-0.03	.771	0.6 (0.1 – 2.8)	.482
onset age of stuttering	*	*	*	0.8 (0.6 – 0.9)	.009

Note: * not applicable