TABLE II. Summary of Clinical Manifestations Obtained From the Second-Stage Survey

	Costello syndrome (%)	CFC syndrome (%)
Total number of patients[a]	43	54
Gender		
Male	17/42 (40)	28/52 (54)
Female	25/42 (60)	24/52 (46)
Genes mutated	*HRAS* 38	*BRAF* 38
	HRAS, 5 but type of mutation unknown	*MAP2K1/2* 8
		KRAS 8
Neoplasia		
Papillomata	7/35 (20)	2/24 (8)
Other tumors	6/34 (18)[b]	5/29 (17)[c]
Growth and development		
Postnatal failure to thrive	41/41 (100)	37/38 (97)
Intellectual disability	39/40 (98)	52/52 (100)
Cardiac defect		
Hypertrophic cardiomyopathy	25/39 (64)[d]	13/50 (26)
Pulmonic stenosis	3/38 (8)	16/51 (31)[e]
Congenital heart malformation[f]	6/39 (15)	13/52 (25)
Arrhythmia	18/41 (44)[d]	10/51 (20)
Central nervous system		
Abnormal brain structure[g]	8/28 (29)	7/23 (30)
Seizure	8/25 (32)	16/33 (48)
Craniofacial characteristics		
Relative macrocephaly	33/39 (85)	31/36 (86)
Musculoskeletal characteristics		
Short stature	18/25 (72)	37/45 (82)
Skin characteristics		
Curly and/or sparse hair	39/41 (95)	38/43 (88)
Soft, loose skin	38/41 (93)[d]	27/37 (73)
Deep palmar/plantar creases	39/41 (95)[d]	29/38 (76)
Outcome		
Alive	38/43 (88)	54/54 (100)
Dead	5/43 (12)[h,d]	0/54 (0)

[a]Number of patients for whom detailed clinical manifestations were obtained in the second-stage survey.
[b]Includes one patient with bladder cancer, two with rhabdomyosarcoma, one with ganglioneuroblastoma, and one with subcutaneous cystic lymphangioma, and one with multiple gallbladder polyps and renal angioma.
[c]Includes one patient with acute lymphoblastic leukemia, one with non-Hodgkin lymphoma, one with hemangioma, and one with calcifying epithelioma.
[d]The frequency of manifestations in patients with Costello syndrome was significantly higher compared with that observed in patients with CFC syndrome ($P < 0.05$ by Fisher's exact test).
[e]The frequency of the manifestation in patients with CFC syndrome was significantly higher compared with that observed in patients with Costello syndrome ($P < 0.05$ by Fisher's exact test).
[f]Includes an atrial septal defect, a ventricular septal defect, a patent ductus arteriosis, a persistent left superior vena cava, and a pulmonary arteriovenous fistula.
[g]Includes a type I Arnold–Chiari malformation, a periventricular leukomalacia, a hydrocephalus, a ventricular dilation, cortical atrophy, a thinning of the corpus callosum, and corpus callosum agenesis.
[h]Cause of death included chronic atrial fibrillation, rhabdomyosarcoma and ganglioneuroblastoma. For two patients, the cause of death is unknown.

We compared the clinical manifestations between patients with *KRAS*, *BRAF*, or *MAP2K1/2* mutations (See Supplemental eTable II in supporting information online). The frequencies of curly hair and hyperkeratosis in patients with *BRAF* mutations were significantly higher than in patients with a *KRAS* mutation. The frequency of hypertrophic cardiomyopathy in patients with *KRAS* mutations was significantly higher than that in patients with *MAP2K1/2* mutations.

DISCUSSION

This is the first nationwide epidemiological study of patients with Costello and CFC syndrome. Before our identification of the genes responsible for Costello and CFC syndromes in 2005 and 2006, only a few Japanese patients with these syndromes had been reported. The availability of molecular analysis facilitated diagnosis of both syndromes, and the number of reports of such patients has steadily increased. In this study, we estimated the prevalence of Costello syndrome and CFC syndrome as 1 in 1,290,000 and 1 in 810,000 in the general population, respectively. The second-stage survey clarified the clinical manifestations of both disorders, including the daily activities of 15 adult patients.

The natural history of Costello and CFC syndromes in adulthood has not been fully clarified. A previous report describing 17 adult patients with Costello syndrome ranging in age from 16 to 40 years showed that all eight individuals who had a bone density measurement taken had abnormal results, suggesting osteoporosis or osteopenia; three of the patients had bone pain, vertebral fractures,

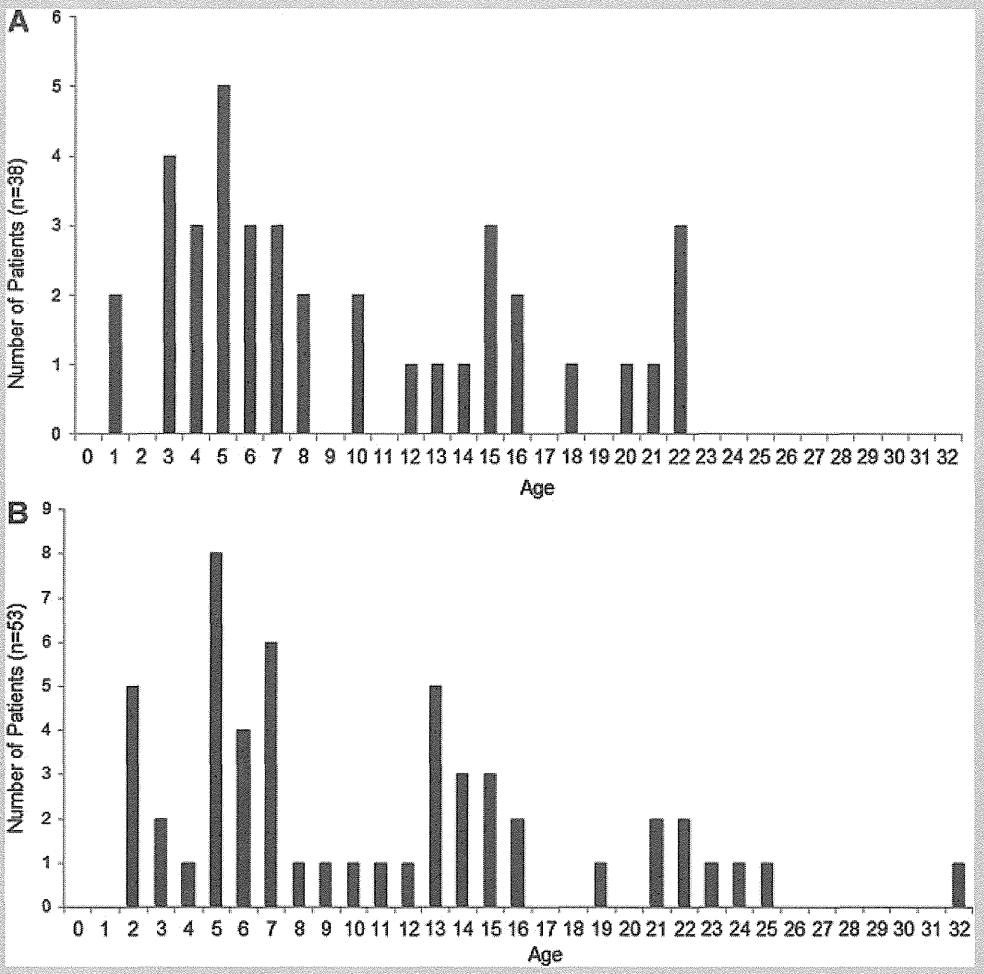

FIG. 2. Age distribution of 38 patients with Costello syndrome (A) and 53 patients with CFC syndrome (B) as of March 31, 2011. Five patients with Costello syndrome were deceased and the age was unknown for one of the 54 patients with CFC syndrome whose clinical manifestations were obtained by the second survey (Table II).

and height loss [White et al., 2005]. A recent study showed the detailed quality of life issues in individuals with Costello syndrome [Hopkins et al., 2010]. Our survey identified the daily activities of six adults with Costello syndrome and nine with CFC syndrome. Although intellectual disability was severe in most patients, 11 adults lived in their houses and did not need constant medical care. Ten of the 15 patients walked independently, and seven could communicate with other people. Thirteen adult patients, not including the two bedridden patients with CFC syndrome, could feed themselves with some assistance. Especially all six patients with Costello syndrome could feed themselves. One had recurrent bladder papillomata and another patient had multiple gallbladder polyps and a renal angioma. None of the examined patients had developed malignant tumors. This survey was unable to identify patients older than 32 years. The tentative prevalence at ages younger than 32 years was estimated to be 1 in 431,000 for Costello syndrome and 1 in 270,000 for CFC syndrome. A follow-up program is important in order to delineate the natural history of older patients.

Our study method has previously been used to estimate the prevalence of intractable diseases, including moyamoya disease, myasthenia gravis, and idiopathic cardiomyopathy [Miura et al., 2002; Kawamura et al., 2006; Kuriyama et al., 2008; Murai et al., 2011] (See Supplemental eTable III in supporting information online). One of the advantages of this survey is that researchers are able to conduct the postal survey without governmental involvement. Another merit of this method is its usefulness for estimating the prevalence of very rare diseases, because we can effectively collect information all over the country, including small hospitals. The response rate from the departments is key to minimizing the standard errors of the estimation. The response rate for our first-stage survey was 76%, which was the highest among the previous eight prevalence studies using this protocol (See Supplemental eTable III in Supporting Information online). However,

TABLE III. Clinical Manifestations and Daily Living Activities in Adult Patients

Patients	**NS30**[a]	**NS125**[b]	**NS157**[b]	**NS239**[b]	**KCC J-210**	**KCC11**	**NS7**[c]	**NS164**
Diagnosis	CS	CS	CS	CS	CS	CS	CFCS	CFCS
Mutation								
Gene	*HRAS*	*HRAS*	*HRAS*	*HRAS*	*HRAS*	*HRAS*	*BRAF*	*BRAF*
Nucleotide substitution	c.38G>A	c.34G>A	c.34G>A	c.34G>A	ND	c.34G>A	c.769C>A	c.770A > G
Amino acid substitution	p.G13D	p.G12S	p.G12S	p.G12S	ND	p.G12S	p.Q257K	p.Q257R
Sex	F	F	F	M	M	M	F	M
Age	18 yr	22 yr	22 yr	22 yr	21 yr	20 yr	32 yr	19 yr
Neoplasia								
Papillomata	Facial papillomata	Nasal papillomata	Bladder papillomata	Facial and hand papillomata	ND	−	−	−
Other tumors	Multiple gallbladder polyps, Renal angioma	−	−	−	ND	−	+ Hemangioma	−
Cardiac defect								
Hypertrophic cardiomyopathy	+	+	+	+	ND	−	−	−
Pulmonic stenosis	−	−	−	−	ND	−	+	+
Congenital heart malformation	−	−	−	−	ND	−	−	−
Arrhythmia	−	−	−	+ Mobitz type II atrioventricular block	ND	−	−	−
Central nervous system								
Abnormal brain structure	ND	−	−	+ Type I Arnold–Chiari malformation	ND	−	−	+ Cortical atrophy
Seizure	ND	−	−	−	ND	+	+	−
Activities of daily living								
Transferring	Cane-assisted gait	Independent	Independent	Independent	Independent	Wheelchair	Independent	Independent
Mental faculties	Severe ID (IQ = 33) (At 4 yr of age)	Severe ID	Moderate ID (IQ44)	Moderate ID (DQ = 35) (At 2 yr of age)	ID (Severity unknown)	Severe ID	Severe ID	Moderate ID (IQ = 37) (At 2 yr of age)
Verbal skills	2-word sentences	2-word sentences	Daily conversation	Daily conversation	ND	Simple conversation	2-word sentences	Single-word utterances
Residence	ND	Home	Home	ND	ND	Home Sometimes using outpatient facilities	Home	Home
School/workplace	Graduated from a school for disabled children; Vocational training facility	Vocational training facility	Vocational training facility	Vocational training facility	ND	None	Graduated from public school class for disabled children	Graduated from a school for disabled children
Other (Feeding, continence)	Self-feeding	Self-feeding	Self-feeding, toileting, and bathing	Self-feeding	Self-feeding	Self-feeding	Almost self-reliant but sometimes needs assistance	Self-feeding, toileting, and bathing

Patients	NS184	NS228	NS233	NS283	KCC U-10	KCC B-1	KCC6	
Diagnosis	CFCS	CFCS	CFCS	CFCS	CFCS	CFCS	CFCS	
Mutation								
Gene	*BRAF*	*BRAF*	*BRAF*	*BRAF*	*BRAF*	*BRAF*	*KRAS*	*BRAF*
Nucleotide substitution	c.770A>G	c.1406G>A	c.770A>G	c.1785T>G	c.770A>G	ND	c.547_552del ACAAAG	c.1390G>A
Amino acid substitution	p.Q257R	p.G469E	p.Q257R	p.F595L	p.Q257R	ND	p.183_184delTK	p.G464R
Sex	F	F	M	F	M	M	F	
Age	22 yr	23 yr	24 yr	21 yr	25 yr	21 yr	22 yr	
Neoplasia								
Papillomata	−	−	−	Cervical papillomata	−	−	ND	
Other tumors	−	−	−	−	−	−	ND	
Cardiac defect								
Hypertrophic cardiomyopathy	−	+	−	−	−	−	+	
Pulmonic stenosis	−	+	−	−	−	+	−	
Congenital heart malformation	−	−	−	−	−	−	−	
Arrhythmia	−	−	−	+ Atrioventricular block	−	−	+ Atrial tachycardia	
Central nervous system								
Abnormal brain structure	+ Periventricular leukomalacia Ventricular dilation	+ Ventricular dilation	−	+ Cortical atrophy White matter volume reduction Thinning of corpus callosum; West syndrome	−	−	ND	
Seizure	+	+	+	+	+	−	ND	
Activities of Daily Living								
Transferring	Independent	Abnormal gait	Independent	Bedridden	Bedridden	Independent	Independent	
Mental faculties	Severe ID	Severe ID	Moderate ID	Very severe ID	Very severe ID	ID (Severity unknown)	ID (Severity unknown)	
Verbal skills	Simple conversation	Daily conversation	Simple conversation	No meaningful word	No meaningful word	Simple conversation	ND	
Residence	Home	Home	Home	Home, Sometimes using outpatient facilities	Home, Sometimes using outpatient facilities	Home	ND	
School/Workplace	Vocational training facility	Vocational training facility	Vocational training facility	None	None	Vocational training facility	ND	
Other (Feeding, Continence)	Self-feeding	Almost self-reliant but sometimes needs assistance	Self-feeding	Full assistance using percutaneous endoscopic gastrostomy	Full assistance	Self-feeding	Self-feeding	

CS, Costello syndrome; CFCS, cardio-facio-cutaneous syndrome; yr, years of age; ID, intellectual disability; IQ, intelligence quotient; DQ, development quotient; ND, not described.
Mutations and a portion of the clinical manifestations have been reported; [a]Aoki et al. [2005]; [b]Niihori et al. [2011]; [c]Narumi et al. [2007].

there are limitations to our survey method. Most survey slips were sent to pediatric departments in general hospitals, which might have precluded identification of adult patients. Another limitation is the possible diagnostic bias of these disorders. In this study, there were major peaks at 5 years of age in both diseases, suggesting that the diagnosis of both disorders is usually made in a certain age range, and patients are less likely to receive the correct diagnosis at a later age. In addition, individuals with Costello syndrome who are mildly or only borderline affected may not be diagnosed by pediatricians at the sampled hospitals [Axelrad et al., 2007]. These effects could lead to a substantial underestimation of the prevalence.

Costello and CFC syndrome fall into the category of rare diseases. To compare the epidemiological features of Costello and CFC syndromes to other genetic disorders, we summarized the results of epidemiologic studies of other genetic disorders (See Supplemental eTable IVin supporting information online). The prevalence and incidence of Sotos syndrome has been reported to be 1 in 20,000 and 1 in 5,000 newborns, respectively [Kurotaki et al., 2003]. A recent nationwide epidemiological study showed that the prevalence of Alexander disease to be 1 in 2,700,000 [Yoshida et al., 2011]. An earlier report estimated the prevalence of Kabuki syndrome at 1 in 32,000 [Niikawa et al., 1988]. Using the similar method with Kabuki syndrome [Niikawa et al., 1988], the incidence of Costello syndrome was estimated to be 1 in 60,000–100,000 (Kurosawa, personal communication). Given that the annual number of live births in Japan is approximately 1,000,000, 10 to 16 patients with Costello syndrome could be born annually. This estimated incidence was higher than the estimated prevalence in patients younger than 32 years of age in our study.

Two mutations in the RAS/MAPK pathway have been identified in a single patient with Noonan syndrome and related disorders [Brasil et al., 2010; Ekvall et al., 2011]. In our study, variations in two molecules that participate in the RAS/MAPK signaling pathway were identified in two patients. One patient had a *SOS1* p.D309Y mutation, which has previously been identified in Noonan syndrome patients [Narumi et al., 2008], and a *K-RAS4A* p.Y166H mutation (a novel variation, inherited from the father). Another patient with CFC syndrome had a *BRAF* p.G464R mutation (known mutation) and a *K-RAS4B* p.T183_ K184del mutation (novel variant). Further study is required to clarify the variations in the RAS pathway that could modify the effect of the disease-causing mutations and the patient phenotypes.

Approximately 13% of patients with Costello syndrome have developed malignant tumors, including rhabdomyosarcomas, ganglioneuroblastomas, and bladder carcinomas [Aoki et al., 2008]. The frequency of malignant tumors in Costello syndrome in the current study was 9% (4 of 43 patients), lower than that reported recently [Lin et al., 2011]. An association between malignant tumors and CFC syndrome was considered rare. However, we identified three patients with CFC syndrome who developed hematologic malignancies [Niihori et al., 2006; Makita et al., 2007; Ohtake et al., 2011], suggesting the importance of molecular diagnoses and careful observation in patients with Costello and CFC syndrome. A tumor screening protocol for patients with Costello syndrome has been proposed [Gripp et al., 2002] and may be useful for patients with CFC syndrome as well. Long-term follow-up is required to determine the incidence and type of tumors in patients with both disorders.

In conclusion, we conducted a nationwide epidemiological survey of patients with Costello and CFC syndrome and estimated the total number of patients with each disease from the results of the postal survey as well as those of molecular analysis. The prevalences of Costello syndrome and CFC syndrome were estimated as 1 in 1,290,000 and 1 in 810,000, respectively. Evaluation of 15 adult patients showed that they had severe intellectual disability but that most of them live at home without constant medical care, suggesting that the number of adult patients may be underestimated. Further epidemiological studies to identify adult patients and follow-up of the patients reported in this study will help us to better understand the natural history of both disorders.

ACKNOWLEDGMENTS

The authors thank the patients and their families who participated in this study. We are also grateful to the physicians who responded to the first and second surveys. We thank Kumi Kato, Riyo Takahashi, and Yoko Tateda for technical assistance. This work was supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan, the Japan Society for the Promotion of Science, and the Ministry of Health, Labour and Welfare of Japan to Y.M. and Y.A.

REFERENCES

Aoki Y, Niihori T, Kawame H, Kurosawa K, Ohashi H, Tanaka Y, Filocamo M, Kato K, Suzuki Y, Kure S, Matsubara Y. 2005. Germline mutations in HRAS proto-oncogene cause Costello syndrome. Nat Genet 37:1038–1040.

Aoki Y, Niihori T, Narumi Y, Kure S, Matsubara Y. 2008. The RAS/MAPK syndromes: Novel roles of the RAS pathway in human genetic disorders. Hum Mutat 29:992–1006.

Axelrad ME, Nicholson L, Stabley DL, Sol-Church K, Gripp KW. 2007. Longitudinal assessment of cognitive characteristics in Costello syndrome. Am J Med Genet Part A 143A:3185–3193.

Brasil AS, Malaquias AC, Wanderley LT, Kim CA, Krieger JE, Jorge AA, Pereira AC, Bertola DR. 2010. Co-occurring PTPN11 and SOS1 gene mutations in Noonan syndrome: Does this predict a more severe phenotype? Arq Bras Endocrinol Metabol 54:717–722.

Cirstea IC, Kutsche K, Dvorsky R, Gremer L, Carta C, Horn D, Roberts AE, Lepri F, Merbitz-Zahradnik T, Konig R, Kratz CP, Pantaleoni F, Dentici ML, Joshi VA, Kucherlapati RS, Mazzanti L, Mundlos S, Patton MA, Silengo MC, Rossi C, Zampino G, Digilio C, Stuppia L, Seemanova E, Pennacchio LA, Gelb BD, Dallapiccola B, Wittinghofer A, Ahmadian MR, Tartaglia M, Zenker M. 2010. A restricted spectrum of NRAS mutations causes Noonan syndrome. Nat Genet 42:27–29.

Cordeddu V, Di Schiavi E, Pennacchio LA, Ma'ayan A, Sarkozy A, Fodale V, Cecchetti S, Cardinale A, Martin J, Schackwitz W, Lipzen A, Zampino G, Mazzanti L, Digilio MC, Martinelli S, Flex E, Lepri F, Bartholdi D, Kutsche K, Ferrero GB, Anichini C, Selicorni A, Rossi C, Tenconi R, Zenker M, Merlo D, Dallapiccola B, Iyengar R, Bazzicalupo P, Gelb BD, Tartaglia M. 2009. Mutation of SHOC2 promotes aberrant protein N-myristoylation and causes Noonan-like syndrome with loose anagen hair. Nat Genet 41:1022–1026.

Costello J. 1971. A new syndrome. NZ Med J 74:397.

Ekvall S, Hagenas L, Allanson J, Anneren G, Bondeson ML. 2011. Co-occurring SHOC2 and PTPN11 mutations in a patient with severe/complex Noonan syndrome-like phenotype. Am J Med Genet Part A 155A:1217–1224.

Gripp KW, Scott CI Jr, Nicholson L, McDonald-McGinn DM, Ozeran JD, Jones MC, Lin AE, Zackai EH. 2002. Five additional Costello syndrome patients with rhabdomyosarcoma: Proposal for a tumor screening protocol. Am J Med Genet 108:80–87.

Hennekam RC. 2003. Costello syndrome: An overview. Am J Med Genet Part C Semin Med Genet 117C:42–48.

Hopkins E, Lin AE, Krepkovich KE, Axelrad ME, Sol-Church K, Stabley DL, Hossain J, Gripp KW. 2010. Living with Costello syndrome: Quality of life issues in older individuals. Am J Med Genet Part A 152A:84–90.

Kawamura T, Nagai M, Tamakoshi A, Hashimoto S, Ohno Y, Nakamura K. 2006. The nationwide epidemiological survey manual for investigating the number of patients and clinico-epidemiological features of intractable diseases, 2nd edition (in Japanese). Tokyo: Japanese Ministry of Health and Welfare.

Kratz CP, Rapisuwon S, Reed H, Hasle H, Rosenberg PS. 2011. Cancer in Noonan, Costello, cardiofaciocutaneous and LEOPARD syndromes. Am J Med Genet Part C Semin Med Genet 157C:83–89.

Kuriyama S, Kusaka Y, Fujimura M, Wakai K, Tamakoshi A, Hashimoto S, Tsuji I, Inaba Y, Yoshimoto T. 2008. Prevalence and clinicoepidemiological features of moyamoya disease in Japan: Findings from a nationwide epidemiological survey. Stroke 39:42–47.

Kurotaki N, Harada N, Shimokawa O, Miyake N, Kawame H, Uetake K, Makita Y, Kondoh T, Ogata T, Hasegawa T, Nagai T, Ozaki T, Touyama M, Shenhav R, Ohashi H, Medne L, Shiihara T, Ohtsu S, Kato Z, Okamoto N, Nishimoto J, Lev D, Miyoshi Y, Ishikiriyama S, Sonoda T, Sakazume S, Fukushima Y, Kurosawa K, Cheng JF, Yoshiura K, Ohta T, Kishino T, Niikawa N, Matsumoto N. 2003. Fifty microdeletions among 112 cases of Sotos syndrome: Low copy repeats possibly mediate the common deletion. Hum Mutat 22:378–387.

Lin AE, Alexander ME, Colan SD, Kerr B, Rauen KA, Noonan J, Baffa J, Hopkins E, Sol-Church K, Limongelli G, Digilio MC, Marino B, Innes AM, Aoki Y, Silberbach M, Delrue MA, White SM, Hamilton RM, O'Connor W, Grossfeld PD, Smoot LB, Padera RF, Gripp KW. 2011. Clinical, pathological, and molecular analyses of cardiovascular abnormalities in Costello syndrome: A Ras/MAPK pathway syndrome. Am J Med Genet Part A 155A:486–507.

Makita Y, Narumi Y, Yoshida M, Niihori T, Kure S, Fujieda K, Matsubara Y, Aoki Y. 2007. Leukemia in Cardio-facio-cutaneous (CFC) syndrome: A patient with a germline mutation in BRAF proto-oncogene. J Pediatr Hematol Oncol 29:287–290.

Miura K, Nakagawa H, Morikawa Y, Sasayama S, Matsumori A, Hasegawa K, Ohno Y, Tamakoshi A, Kawamura T, Inaba Y. 2002. Epidemiology of idiopathic cardiomyopathy in Japan: Results from a nationwide survey. Heart 87:126–130.

Murai H, Yamashita N, Watanabe M, Nomura Y, Motomura M, Yoshikawa H, Nakamura Y, Kawaguchi N, Onodera H, Araga S, Isobe N, Nagai M, Kira J. 2011. Characteristics of myasthenia gravis according to onset-age: Japanese nationwide survey. J Neurol Sci 305:97–102.

Narumi Y, Aoki Y, Niihori T, Neri G, Cave H, Verloes A, Nava C, Kavamura MI, Okamoto N, Kurosawa K, Hennekam RC, Wilson LC, Gillessen-Kaesbach G, Wieczorek D, Lapunzina P, Ohashi H, Makita Y, Kondo I, Tsuchiya S, Ito E, Sameshima K, Kato K, Kure S, Matsubara Y. 2007. Molecular and clinical characterization of cardio-facio-cutaneous (CFC) syndrome: Overlapping clinical manifestations with Costello syndrome. Am J Med Genet Part A 143A:799–807.

Narumi Y, Aoki Y, Niihori T, Sakurai M, Cave H, Verloes A, Nishio K, Ohashi H, Kurosawa K, Okamoto N, Kawame H, Mizuno S, Kondoh T, Addor MC, Coeslier-Dieux A, Vincent-Delorme C, Tabayashi K, Aoki M, Kobayashi T, Guliyeva A, Kure S, Matsubara Y. 2008. Clinical manifestations in patients with SOS1 mutations range from Noonan syndrome to CFC syndrome. J Hum Genet 53:834–841.

Nava C, Hanna N, Michot C, Pereira S, Pouvreau N, Niihori T, Aoki Y, Matsubara Y, Arveiler B, Lacombe D, Pasmant E, Parfait B, Baumann C, Heron D, Sigaudy S, Toutain A, Rio M, Goldenberg A, Leheup B, Verloes A, Cave H. 2007. Cardio-facio-cutaneous and Noonan syndromes due to mutations in the RAS/MAPK signalling pathway: Genotype-phenotype relationships and overlap with Costello syndrome. J Med Genet 44: 763–771.

Niihori T, Aoki Y, Narumi Y, Neri G, Cave H, Verloes A, Okamoto N, Hennekam RC, Gillessen-Kaesbach G, Wieczorek D, Kavamura MI, Kurosawa K, Ohashi H, Wilson L, Heron D, Bonneau D, Corona G, Kaname T, Naritomi K, Baumann C, Matsumoto N, Kato K, Kure S, Matsubara Y. 2006. Germline KRAS and BRAF mutations in cardio-facio-cutaneous syndrome. Nat Genet 38:294–296.

Niihori T, Aoki Y, Okamoto N, Kurosawa K, Ohashi H, Mizuno S, Kawame H, Inazawa J, Ohura T, Arai H, Nabatame S, Kikuchi K, Kuroki Y, Miura M, Tanaka T, Ohtake A, Omori I, Ihara K, Mabe H, Watanabe K, Niijima S, Okano E, Numabe H, Matsubara Y. 2011. HRAS mutants identified in Costello syndrome patients can induce cellular senescence: Possible implications for the pathogenesis of Costello syndrome. J Hum Genet 56:707–715.

Niikawa N, Kuroki Y, Kajii T, Matsuura N, Ishikiriyama S, Tonoki H, Ishikawa N, Yamada Y, Fujita M, Umemoto H., et al. 1988. Kabuki make-up (Niikawa-Kuroki) syndrome: A study of 62 patients. Am J Med Genet 31:565–589.

Ohtake A, Aoki Y, Saito Y, Niihori T, Shibuya A, Kure S, Matsubara Y. 2011. Non-Hodgkin Lymphoma in a Patient With Cardiofaciocutaneous Syndrome. J Pediatr Hematol Oncol 33:e342–e346.

Pandit B, Sarkozy A, Pennacchio LA, Carta C, Oishi K, Martinelli S, Pogna EA, Schackwitz W, Ustaszewska A, Landstrom A, Bos JM, Ommen SR, Esposito G, Lepri F, Faul C, Mundel P, Lopez Siguero JP, Tenconi R, Selicorni A, Rossi C, Mazzanti L, Torrente I, Marino B, Digilio MC, Zampino G, Ackerman MJ, Dallapiccola B, Tartaglia M, Gelb BD. 2007. Gain-of-function RAF1 mutations cause Noonan and LEOPARD syndromes with hypertrophic cardiomyopathy. Nat Genet 39:1007–1012.

Rauen KA. 2007. Cardiofaciocutaneous syndrome. In: GeneReviews at GeneTests: Medical genetics information resource [online database]. Seattle: University of Washington.

Razzaque MA, Nishizawa T, Komoike Y, Yagi H, Furutani M, Amo R, Kamisago M, Momma K, Katayama H, Nakagawa M, Fujiwara Y, Matsushima M, Mizuno K, Tokuyama M, Hirota H, Muneuchi J, Higashinakagawa T, Matsuoka R. 2007. Germline gain-of-function mutations in RAF1 cause Noonan syndrome. Nat Genet 39:1013–1017.

Reynolds JF, Neri G, Herrmann JP, Blumberg B, Coldwell JG, Miles PV, Opitz JM. 1986. New multiple congenital anomalies/mental retardation syndrome with cardio-facio-cutaneous involvement–the CFC syndrome. Am J Med Genet 25:413–427.

Roberts AE, Araki T, Swanson KD, Montgomery KT, Schiripo TA, Joshi VA, Li L, Yassin Y, Tamburino AM, Neel BG, Kucherlapati RS. 2007. Germline gain-of-function mutations in SOS1 cause Noonan syndrome. Nat Genet 39:70–74.

Rodriguez-Viciana P, Tetsu O, Tidyman WE, Estep AL, Conger BA, Cruz MS, McCormick F, Rauen KA. 2006. Germline mutations in genes within the MAPK pathway cause cardio-facio-cutaneous syndrome. Science 311:1287–1290.

Satoh K, Shimosegawa T, Masamune A, Hirota M, Kikuta K, Kihara Y, Kuriyama S, Tsuji I, Satoh A, Hamada S. 2011. Nationwide epidemiological survey of acute pancreatitis in Japan. Pancreas 40:503–507.

Schubbert S, Zenker M, Rowe SL, Boll S, Klein C, Bollag G, van der Burgt I, Musante L, Kalscheuer V, Wehner LE, Nguyen H, West B, Zhang KY, Sistermans E, Rauch A, Niemeyer CM, Shannon K, Kratz CP. 2006. Germline KRAS mutations cause Noonan syndrome. Nat Genet 38: 331–336.

Tartaglia M, Mehler EL, Goldberg R, Zampino G, Brunner HG, Kremer H, van der Burgt I, Crosby AH, Ion A, Jeffery S, Kalidas K, Patton MA, Kucherlapati RS, Gelb BD. 2001. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. Nat Genet 29:465–468.

Tartaglia M, Pennacchio LA, Zhao C, Yadav KK, Fodale V, Sarkozy A, Pandit B, Oishi K, Martinelli S, Schackwitz W, Ustaszewska A, Martin J, Bristow J, Carta C, Lepri F, Neri C, Vasta I, Gibson K, Curry CJ, Siguero JP, Digilio MC, Zampino G, Dallapiccola B, Bar-Sagi D, Gelb BD. 2007. Gain-of-function SOS1 mutations cause a distinctive form of Noonan syndrome. Nat Genet 39:75–79.

Teranishi M, Katayama N, Uchida Y, Tominaga M, Nakashima T. 2007. Thirty-year trends in sudden deafness from four nationwide epidemiological surveys in Japan. Acta Otolaryngol 127:1259–1265.

Tidyman WE, Rauen KA. 2009. The RASopathies: Developmental syndromes of Ras/MAPK pathway dysregulation. Curr Opin Genet Dev 19:230–236.

White SM, Graham JM Jr, Kerr B, Gripp K, Weksberg R, Cytrynbaum C, Reeder JL, Stewart FJ, Edwards M, Wilson M, Bankier A. 2005. The adult phenotype in Costello syndrome. Am J Med Genet Part A 136A:128–135.

Yoshida T, Sasaki M, Yoshida M, Namekawa M, Okamoto Y, Tsujino S, Sasayama H, Mizuta I, Nakagawa M. 2011. Nationwide survey of Alexander disease in Japan and proposed new guidelines for diagnosis. J Neurol 258:1998–2008.

Clinical and Experimental Hypertension, 2012; 34(4): 290–296

ISSN 1064-1963 print/1525-6006 online
DOI: 10.3109/10641963.2012.681086

informa
healthcare

Daily Serial Hemodynamic Data During Pregnancy and Seasonal Variation: The BOSHI Study

Hirohito Metoki,[1,2] Takayoshi Ohkubo,[3] Taku Obara,[1,4] Konomi Akutsu,[5] Mami Yamamoto,[1,2] Mami Ishikuro,[1,4] Kasumi Sakurai,[1,6] Noriyuki Iwama,[2] Mikiko Katagiri,[2] Junichi Sugawara,[2] Takuo Hirose,[3,5] Michihiro Sato,[3,5] Masahiro Kikuya,[3] Katsuyo Yagihashi,[7] Yoichi Matsubara,[8] Nobuo Yaegashi,[1,2] Shigeru Mori,[7] Masakuni Suzuki,[7] Yutaka Imai,[3] and the BOSHI Study Group

[1]*Environment and Genome Research Center, Tohoku University Graduate School of Medicine, Sendai, Japan,* [2]*Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, Sendai, Japan,* [3]*Department of Planning for Drug Development and Clinical Evaluation, Tohoku University Graduate School of Pharmaceutical Sciences, Sendai, Japan,* [4]*Department of Molecular Epidemiology, Tohoku University Graduate School of Medicine, Sendai, Japan,* [5]*Department of Clinical Pharmacology and Therapeutics, Tohoku University Graduate School of Pharmaceutical Sciences, Sendai, Japan,* [6]*Department of Environmental Health Sciences, Tohoku University Graduate School of Medicine, Sendai, Japan,* [7]*Suzuki Memorial Hospital, Iwanuma, Japan,* [8]*Department of Medical genetics, Tohoku University Graduate School of Medicine, Sendai, Japan*

Abstract

Although there are some reports that low plasma volume or increased cardiac output is associated with developing preeclampsia, there are few reports of daily serial hemodynamic data during pregnancy. A total of 37 092 home blood pressure (BP) and heart rate (HR) measurements were obtained from 425 normal pregnant women. Heart rate and shock index (SI) gradually increased by gestational week 32 and then decreased, whereas double product (DP) increased linearly during pregnancy. Although systolic BP and DP were consistently and negatively correlated with daily minimum outside temperature, HR and SI were positively correlated with minimum outside temperature in summer.

Keywords: clinical science, blood pressure measurement/monitoring, preeclampsia/pregnancy, self-monitoring of blood pressure

INTRODUCTION

Gestational hypertension and preeclampsia are common disorders during pregnancy, with the majority of cases developing at or near term (1). Plasma volume is significantly lower in preeclampsia than in normal pregnancy at a gestational age of 14–17 weeks (2). Recently, it has been reported that cardiac output is increased in the first trimester in women who develop preeclampsia (3,4). Although hemodynamic changes during pregnancy appear to be important, there are few reports dealing with daily serial hemodynamic changes during pregnancy.

Heart rate (HR), double product (DP), which is calculated from systolic blood pressure (SBP) multiplied by HR, and shock index (SI), which is calculated from HR divided by SBP, are parameters that are easy to obtain from blood pressure (BP) measurements. Double product is a surrogate measure of myocardial oxygen demand and cardiac workload, which has recently become widely used in cardiovascular medicine (5). Shock index is an index to determine hypovolemia, which is accompanied by hypotension and tachycardia (6,7), and it predicts the quantity of hemorrhage from a ruptured ectopic pregnancy better than HR or SBP alone (6). Birkhahn et al. reported that acute blood loss of 450 mL significantly increased SI from 0.61 to 0.65 bpm/mm Hg (7).

Although home BP measurement has been recognized as an important tool among pregnant women (8,9), data derived from home BP measurements are rare. The guidelines for hypertension in pregnancy do not mention home BP measurements (10–12). We have previously reported the associations among home BP, gestational age, and seasonal variation (13). The aim of this study was to collect daily serial hemodynamic data (HR, DP, and SI) during pregnancy with adjustment for gestational age and seasonal variation using home measurements of BP and HR.

Address correspondence to Hirohito Metoki, MD, PhD, Environment and Genome Research Center, Tohoku University Graduate School of Medicine, 2-1 Seiryo-cho, Aoba-ku, Sendai, Miyagi 980-8575, Japan. E-mail: hmetoki@med.tohoku.ac.jp

Received 31 August 2011; revised 4 October 2011; accepted 25 October 2011.

METHODS

The present report is a part of the Babies and their Parents' Longitudinal Observation in Suzuki Memorial Hospital on Intrauterine Period (BOSHI) study (13). The study was conducted at Suzuki Memorial Hospital, which is the only hospital specializing in obstetrics, gynecology, and in vitro fertilization in the Sendai City area of Miyagi Prefecture, Japan. Sendai is the central city of northeastern Japan. There were 1098 births in Suzuki Memorial Hospital in 2006. All study protocols were approved by the Institutional Review Board of Tohoku University School of Medicine and by the Hospital Review Board of Suzuki Memorial Hospital.

In Japan, the interval for medical checkups during pregnancy is once every 4 weeks until week 23, once every 2 weeks until week 35, and once a week after 36 weeks.

Only healthy pregnant women before gestational week 20 with no history of hypertension and who could measure their home BP during pregnancy were included after obtaining their written informed consent. Gestational age was calculated by last menstrual period with correction for crown-lump length before 12 weeks of gestation. After delivery, the obstetrician and physician verified that the pregnancy had been normal without hypertension or proteinuria.

Subjects

A total of 3362 women were diagnosed as being pregnant between October 1, 2006 and September 30, 2009 and reserved delivery in the hospital. All of these women were invited to participate by a poster and a letter from the investigating staff; 1032 women received an explanation of the research from a physician, pharmacist, or midwife.

Daily Serial Hemodynamic Data Using Home BP Measurements

Home BP was measured using an HEM-747IC or HEM-7080IC semiautomatic device (Omron Healthcare, Kyoto, Japan) based on the cuff-oscillometric method, which generates a digital display of not only both SBP and diastolic BP (14) but also HR. Double product was calculated from SBP multiplied by HR, and SI was calculated from HR divided by SBP.

Physicians, pharmacists, and midwives instructed subjects on how to perform home BP measurements. On the basis of the Japanese Society of Hypertension guidelines for self-monitoring of BP at home (15), the subjects were asked to measure their home BP every morning within 1 hour of waking, after micturition, before breakfast, while seated, and after resting for more than 1 minute and to keep recording their home BP until 1 month after delivery.

Meteorological Data

Meteorological data measured at Sendai Meteorological Observatory for the period during which home BP measurements were included: daily minimum, maximum, and mean outside temperatures; daily mean atmospheric pressure; relative humidity; and duration of sunshine. Normalized data were also obtained from Sendai Meteorological Observatory as averaged meteorological data from 1970 to 2000.

Statistical Analysis

Daily serial hemodynamic data (SBP, HR, DP, and SI) were examined using a mixed linear model with gestational age as the fixed effect and subjects as the random effect. When we adjusted for seasonal effect, meteorological data were also regarded as fixed effect. We further examined yearly variation of daily serial hemodynamic data; we examined weekly serial hemodynamic data in a year without adjustment for meteorological data. The measurement week of the year was regarded as a fixed effect in a mixed model.

We analyzed data using the SAS package (version 9.2, SAS Institute Inc., Cary, NC, USA). Values are expressed as mean ± SD and least square means were calculated by the mixed linear model and expressed as mean with their 95% confidence intervals (CI; Figures 1 and 2).

A sample size of 387 women was required to estimate the distribution of mean home BP values within a ±0.8 mm Hg range at a 95% CI, assuming that the SD of home BP values in pregnant women is 8 mm Hg based on the previous report (13).

RESULTS

Subjects

A total of 518 women finally entered the study. Nine women were excluded due to fetal death in the first trimester. Another four women were transferred to other hospitals because of threatened premature delivery (two women), premature rupture of the membranes (one woman), and diabetes (one woman). One woman was excluded because she transferred to the nearest midwifery clinic. During the follow-up period, 51 women developed gestational hypertension or preeclampsia and were excluded. Among the remaining 452 healthy pregnant women, home BP monitoring was not available for 27 women during pregnancy. Data of the remaining 425 healthy pregnant women were analyzed.

The mean age of the 425 healthy pregnant women analyzed in this study was 31.3 ± 4.6 years at entry. Their mean height, weight, and BMI were 158.4 ± 5.3 cm, 54.2 ± 9.0 kg, and 21.6 ± 3.4 kg/m^2, respectively. The frequency of ever smokers was 16.8% and that of ever drinkers was 50.7%. Among them, 71% of ever smokers and 95% of ever drinkers stopped during pregnancy. The mean birth weight of their children was 3054 ± 394 g.

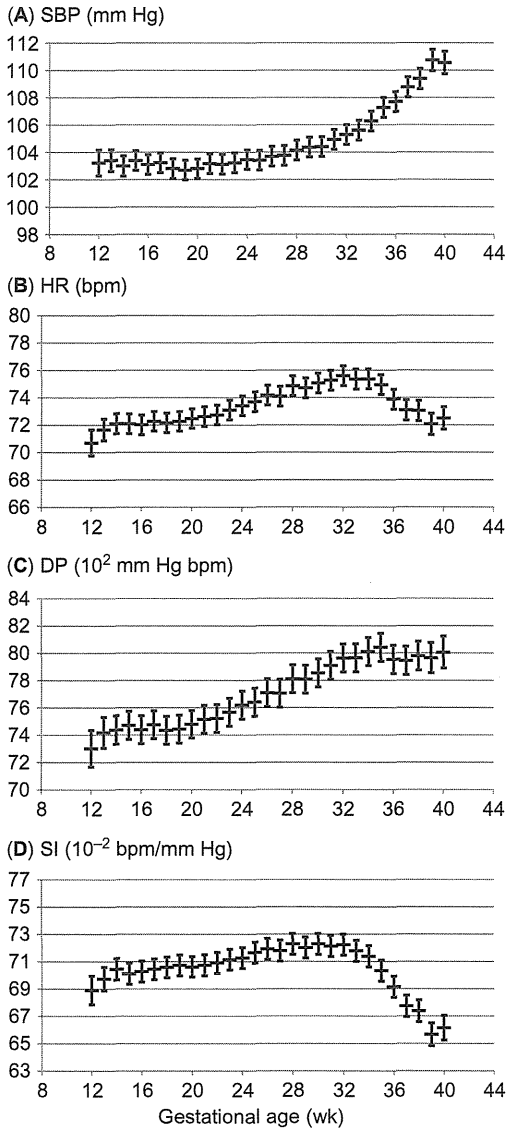

Figure 1. (**A**) Systolic blood pressure (SBP), (**B**) heart rate (HR), (**C**) double product (DP), and (**D**) shock index (SI) values and their 95% confidence intervals for each week of gestational age, calculated on the basis of a mixed linear model.

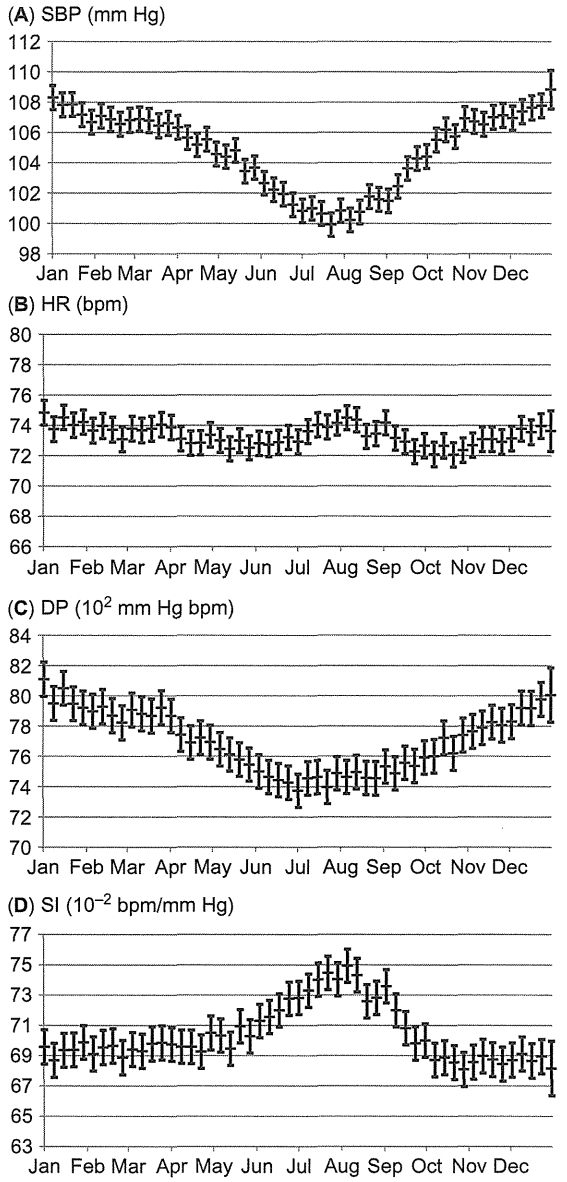

Figure 2. (**A**) Systolic blood pressure (SBP), (**B**) heart rate (HR), (**C**) double product (DP), and (**D**) shock index (SI) values and their 95% confidence intervals for each week for a year, calculated on the basis of a mixed linear model without adjusting for seasonal variation.

Daily Serial Hemodynamic Data and Gestational Age

The association between SBP, HR, DP, SI, and gestational age using a mixed linear model without adjusting for meteorological data is shown in Figure 1. Heart rate and SI increased gradually, reaching peak values at gestational week 33, while DP increased linearly from the first trimester to the third trimester.

After adjusting for meteorological data, the associations between these daily hemodynamic data and gestational age showed the same tendency (data not shown).

Daily Serial Hemodynamic Data and Seasonal Variation

The yearly variation in SBP, HR, DP, and SI calculated using a mixed linear model adjusting for gestational age is shown in Figure 2. Systolic blood pressure decreased gradually from January to August and gradually increased from August to December. Heart rate decreased gradually from January to June, after which it increased and reached its peak value in August. Double product was the highest in January and decreased to its lowest value in June. From June to December, DP increased gradually. Although SI was stable from January to June and from October to December, it increased from June to August, reached its peak in August, and then decreased to October.